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and pharmacological characterization of 2-
hydroxy-3-((2-carboxyethyl)trio)-3-(2-(8-
phenyl-octyl)phenyl)propanoic acid"**

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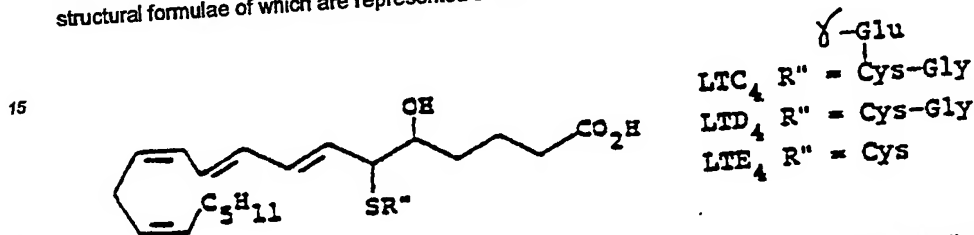
EP 0 296 732 B1

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Description

"Slow Reacting Substance of Anaphylaxis" (SRS-A) has been shown to be a highly potent bronchoconstricting substance which is released primarily from mast cells and basophils on antigenic challenge. SRS-A has been proposed as a primary mediator in human asthma. SRS-A, in addition to its pronounced effects on lung tissue, also produces permeability changes in skin and may be involved in acute cutaneous allergic reactions. Further, SRS-A has been shown to effect depression of ventricular contraction and potentiation of the cardiovascular effects of histamine.

The discovery of the naturally occurring leukotrienes and their relationship to SRS-A has reinforced interest in SRS-A and other arachidonate metabolites. SRS-A derived from mouse, rat, guinea pig and man have all been characterized as mixtures of leukotriene-C₄ (LTC₄), leukotriene-D₄ (LTD₄) and leukotriene-E₄ (LTE₄), the structural formulae of which are represented below.



Leukotrienes are a group of eicosanoids formed from arachidonic acid metabolism via the lipoxygenase pathway. These lipid derivatives originate from LTA₄ and are of two types: (1) those containing a sulfido-peptide side chain (LTC₄, LTD₄, and LTE₄), and (2) those that are nonpeptidic (LTB₄). Leukotrienes comprise a group of naturally occurring substances that have the potential to contribute significantly to the pathogenesis of a variety of inflammatory and ischemic disorders. The pathophysiological role of leukotrienes has been the focus of recent intensive studies.

As summarized by Left, A.M., *Biochemical Pharmacology*, 35, 2, 123-127 (1986) both the peptide and non-peptide leukotrienes exert microcirculatory actions, promoting leakage of fluid across the capillary endothelial membrane in most types of vascular beds. LTB₄ has potent chemotactic actions and contributes to the recruitment and adherence of mobile scavenger cells to the endothelial membrane. LTC₄, LTD₄ and LTE₄ stimulate a variety of types of muscles. LTC₄ and LTD₄ are potent bronchoconstrictors and effective stimulators of vascular smooth muscle. This vasoconstrictor effect has been shown to occur in pulmonary, coronary, cerebral, renal, and mesenteric vasculatures.

Leukotrienes have been implicated in a number of pulmonary diseases. Leukotrienes are known to be potent bronchoconstrictors in humans. LTC₄ and LTD₄ have been shown to be potent and selective peripheral airway agonists, being more active than histamine. [See Drazen, J.M. et al., *Proc. Nat'l. Acad. Sci. USA*, 77, 7435-7438 (1980).] LTC₄ and LTD₄ have been shown to increase the release of mucus from human airways *in vitro*. [See Marom, Z. et al., *Am. Rev. Respir. Dis.*, 126, 449-451 (1982).] The leukotriene antagonists of the present invention can be useful in the treatment of allergic or non-allergic bronchial asthma or pulmonary anaphylaxis.

The presence of leukotrienes in the sputum of patients having cystic fibrosis, chronic bronchitis, and bronchiectasis at levels likely to have pathophysiological effects has been demonstrated by Zakrzewski et al. [See Zakrzewski, J.T. et al., *Prostaglandins*, 28, 5, 641 (1984).] Treatment of these diseases constitutes additional possible utility for leukotriene antagonists.

Leukotrienes have been identified in the nasal secretions of allergic subjects who underwent *in vivo* challenge with specific antigen. The release of the leukotrienes was correlated with typical allergic signs and symptoms. [See Creticos, P.S. et al., *New England J. of Med.*, 310, 25, 1626-1629 (1984).] This suggests that allergic rhinitis is another area of utility for leukotriene antagonists.

The role of leukotrienes and the specificity and selectivity of a particular leukotriene antagonist in an animal model of the adult respiratory distress syndrome was investigated by Snapper et al. [See Snapper, J.R. et al., *Abstracts of Int'l Conf. on Prostaglandins and Related Comp.*, Florence, Italy, p. 495 (June 1986).] Elevated concentrations of LTD₄ were shown in pulmonary edema fluid of patients with adult respiratory distress syndrome. [See Matthay, M. et al. *J. Clin. Immunol.*, 4, 479-483 (1981).] Markedly elevated leukotriene levels have been shown in the edema fluid of a patient with pulmonary edema after cardiopulmonary bypass. [See Swerdlow, B.N., et al., *Anesth. Analg.*, 65, 306-308, (1986).] LTC and LTD have also been shown to have a direct systemic arterial hypotensive effect and produce vasoconstriction and increased vasopermeability. [See Drazen et al., *ibid.*] This suggests leukotriene antagonists can also be useful in the areas of adult respiratory

distress syndrome, pulmonary edema, and hypertension.

Leukotrienes have also been directly or indirectly implicated in a variety of non-pulmonary diseases in the ocular, dermatologic, cardiovascular, renal, trauma, inflammatory, carcinogenic and other areas.

Further evidence of leukotrienes as mediators of allergic reactions is provided by the identification of leukotrienes in tear fluids from subjects following a conjunctival provocation test and in skin blister fluids after allergen challenge in allergic skin diseases and conjunctival mucosa. [See Bisgaard, H., et al., *Allergy*, 40, 417-423 (1985).] Leukotriene immunoreactivity has also been shown to be present in the aqueous humor of human patients with and without uveitis. The concentrations of leukotrienes were sufficiently high that these mediators were expected to contribute in a meaningful way to tissue responses. [See Parker, J.A. et al., *Arch Ophthalmol*, 104, 722-724 (1986).] It has also been demonstrated that psoriatic skin has elevated levels of leukotrienes. [See Ford-Hutchinson, J., *Allergy Clin. Immunol.*, 74, 437-440 (1984).] Local effects of intracutaneous injections of synthetic leukotrienes in human skin were demonstrated by Soter et al. [See Soter et al. *J. Clin Invest Dermatol*, 80, 115-119 (1983).] Cutaneous vasodilation with edema formation and a neutrophil infiltrate were induced. Leukotriene synthesis inhibitors or leukotriene antagonists can also be useful in the treatment of ocular or dermatological diseases such as allergic conjunctivitis, uveitis, allergic dermatitis or psoriasis.

Another area of utility for leukotriene antagonists is in the treatment of cardiovascular diseases. Since peptide leukotrienes are potent coronary vasoconstrictors, they are implicated in a variety of cardiac disorders including arrhythmias, conduction blocks and cardiac depression. Synthetic leukotrienes have been shown to be powerful myocardial depressants, their effects consisting of a decrease in contractile force and coronary flow. The cardiac effects of LTC₄ and LTD₄ have been shown to be antagonized by a specific leukotriene antagonist, thus suggesting usefulness of leukotriene antagonists in the areas of myocardial depression and cardiac anaphylaxis. [See Burke, J.A., et al., *J. Pharmacology and Experimental Therapeutics*, 221, 1, 235-241 (1982).]

LTC₄ and LTD₄ have been measured in the body fluids of rats in endotoxic shock, but are rapidly cleared from the blood into the bile. Thus leukotrienes are formed in ischemia and shock. Specific inhibitors of leukotriene biosynthesis reduce the level of leukotrienes and therefore reduce manifestations of traumatic shock, endotoxic shock, and acute myocardial ischemia. Leukotriene receptor antagonists have also been shown to reduce manifestations of endotoxic shock and to reduce extension of infarct size. Administration of peptide leukotrienes has been shown to produce significant ischemia or shock. [See Lefer, A.M., *Biochemical Pharmacology*, 35, 2, 123-127 (1986).] Thus further areas of utility for leukotriene antagonists can be the treatment of myocardial ischemia, acute myocardial infarction, salvage of ischemic myocardium, angina, cardiac arrhythmias, shock and atherosclerosis.

Leukotriene antagonists can also be useful in the area of renal ischemia or renal failure. Badr et al. have shown that LTC₄ produces significant elevation of mean arterial pressure and reductions in cardiac output and renal blood flow, and that such effects can be abolished by a specific leukotriene antagonist. [See Badr, K.R. et al., *Circulation Research*, 54, 5, 492-499 (1984).] Leukotrienes have also been shown to have a role in endotoxin-induced renal failure and the effects of the leukotrienes selectively antagonized in this model of renal injury. [See Badr, K.F., et al., *Kidney International*, 30, 474-480 (1986).] LTD₄ has been shown to produce local glomerular constrictor actions which are prevented by treatment with a leukotriene antagonist. [See Badr, K.F. et al., *Kidney International*, 29, 1, 328 (1986).] LTC₄ has been demonstrated to contract rat glomerular mesangial cells in culture and thereby effect intraglomerular actions to reduce filtration surface area. [See Dunn, M.J. et al., *Kidney International*, 27, 1, 256 (1985).] Thus another area of utility for leukotriene antagonists can be in the treatment of glomerulonephritis.

Leukotrienes have also been indicated in the area of transplant rejection. An increase in cardiac and renal allograft survival in the presence of a leukotriene receptor antagonist was documented by Foegh et al. [See Foegh, M.L. et al. *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*, 13, 209-217 (1985).] Rejection of rat renal allografts was shown to produce increased amounts of LTC₄. [See Coffman, T.M. et al., *Kidney International*, 29, 1, 332 (1986).]

A further area of utility for leukotriene antagonists can be in treatment of tissue trauma, burns, or fractures. A significant increase in the production of cysteinyl leukotrienes was shown after mechanical or thermal trauma sufficient to induce tissue edema and circulatory and respiratory dysfunction. [See Denzinger, C. et al., *Science*, 230, 330-332 (1985).]

Leukotrienes have also been shown to have a role in acute inflammatory actions. LTC₄ and LTD₄ have potent effects on vascular caliber and permeability and LTB₄ increases leukocyte adhesion to the endothelium. The arteriolar constriction, plasma leakage, and leukocyte adhesion bear close resemblance to the early events in acute inflammatory reactions. [See Dahlen, S.E. et al., *Proc. Natl. Acad. Sci. USA*, 78, 6, 3887-3891 (1981).] Mediation of local homeostasis and inflammation by leukotrienes and other mast cell-dependent compounds was also investigated by Lewis et al. [See Lewis, R.A. et al., *Nature*, 293, 103-108 (1981).] Leukotriene antagon-

ists can therefore be useful in the treatment of inflammatory diseases including rheumatoid arthritis and gout.

Cysteinyl leukotrienes have also been shown to undergo enterohepatic circulation, and thus are indicated in the area of inflammatory liver disease. [See Denzinger, C. et al., Prostaglandins Leukotrienes and Medicine, 21, 321-322 (1986).] Leukotrienes can also be important mediators in inflammation of inflammatory bowel disease. [See Peskar, B.M. et al., Agents and Actions, 18, 381-383 (1986).] Leukotriene antagonists thus can be useful in the treatment of inflammatory liver and bowel disease.

Leukotrienes have been shown to modulate IL-1 production by human monocytes. [See Rola-Pleszczynski, M. et al., J. of Immun., 135, 6, 3958-3961 (1985).] This suggests that leukotriene antagonists may play a role in IL-1 mediated functions of monocytes in inflammation and immune reactions.

LTA₄ has been shown to be a factor in inducing carcinogenic tumors and is considered a link between acute immunologic defense reactions and carcinogenesis. Leukotriene antagonists can therefore possibly have utility in treatment of some types of carcinogenic tumors. [See Wischnewsky, G.G. et al. Anticancer Res. 5, 6, 639 (1985).]

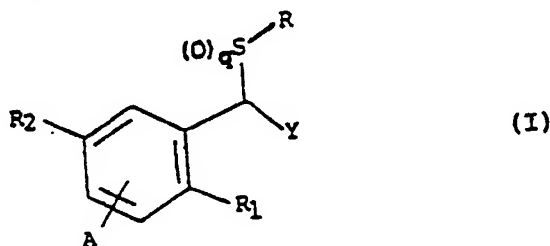
Leukotrienes have been implicated in gastric cytodestruction and gastric ulcers. Damage of gastro-intestinal mucosa because of potent vasoconstriction and stasis of blood flow is correlated with increased levels of LTC₄. Functional antagonism of leukotriene effects may represent an alternative in treatment of mucosal injury. [See Dreyling, K.W. et al., British J. Pharmacology, 88, 236P (1986), and Peskar, B.M. et al. Prostaglandins, 31, 2, 283-293 (1986).] A leukotriene antagonist has been shown to protect against stress-induced gastric ulcer in rats. [See Ogle, C.W. et al., IRCS Med. Sci., 14, 114-115 (1986).]

Other areas in which leukotriene antagonists can have utility because leukotrienes are indicated as mediators include prevention of premature labor [See Clayton, J.K. et al., Proceedings of the BPS, 573P, 17-19 Dec. 1984]; treatment of migraine headaches [See Gazzaniga, P.P. et al., Abstracts Int'l Conf. on Prostaglandins and Related Comp., 121, Florence, Italy (June 1986)]; and treatment of gallstones [See Doty, J.E. et al., Amer. J. of Surgery, 145, 54-61 (1983) and Marom, Z. et al., Amer. Rev. Respir. Dis., 126, 449-451 (1982).

By antagonizing the effects of LTC₄, LTD₄ and LTE₄ or other pharmacologically active mediators at the end organ, for example, airway smooth muscle, the compounds and pharmaceutical compositions of the instant invention are valuable in the treatment of diseases in subjects, including human or animals, in which leukotrienes are a key factor.

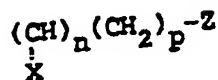
SUMMARY OF THE INVENTION

This invention relates to compounds represented by structural formula (I)



wherein

- q is 0, 1, or 2 ;
- R₁ is (L)_a-(CH₂)_b-(T)_c-M
- a is 0 or 1 ;
- b is 3 to 14 ;
- c is 0 or 1 ;
- L and T are independently sulfur, oxygen, or CH₂ with the proviso that L and T are not sulfur and q is 1 or 2 ; and
- M is C₁₋₄ alkyl, ethynyl, trifluoromethyl, isopropenyl, furanyl, thienyl, cyclohexyl or phenyl optionally mono-substituted with Br, Cl, CF₃, C₁₋₄ alkoxy, C₁₋₄ alkyl, methylthio, or trifluoromethylthio ;
- R₂ are A are independently selected from H, CF₃, C₁₋₄ alkyl, C₁₋₄ alkoxy, F, Cl, Br, I, OH, NO₂ or NH₂ ;
- or R₁ and A are H and
- R₂ is (L)_a-(CH₂)_b-(T)_c-M wherein a, b, c, L, T, and M are as defined above ;
- Y is COR₃ or



wherein

R_3 is OH, NH_2 , aryloxy, or C_{1-6} alkoxy ;

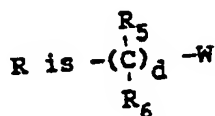
n is 0 or 1 ;

p is 0, 1 or 2 ;

X is H, OH, C_{1-4} alkyl, C_{1-4} alkoxy,

or F ; and

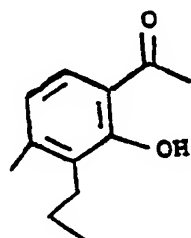
Z is COR_3 , or tetrazolyl ;



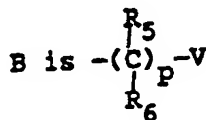
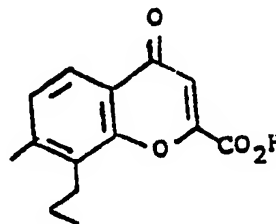
R_5 and R_6 are each independently hydrogen or C_{1-4} alkyl at any point when d is not 0 ;

d is 0 to 6 ;

W is a six membered aryl or heteroaryl ring selected from phenyl, pyridyl, or pyrimidyl, unsubstituted or substituted with B, C, or D, or W is one of



or



wherein R_5 and R_6 are each independently hydrogen or C_{1-4} alkyl ; p is 0 to 6 ; V is H, C_{1-4} alkyl, COR_3 , SO_3H , SO_2H , SO_2NH_2 , COCH_2OH , CHOHCH_2OH , or tetrazolyl, with R_3 as defined above ;

C and D are independently selected from H, OH, F, Cl, Br, CF_3 , C_{1-4} alkyl, C_{1-4} alkoxy, methylthio, trifluoromethylthio, NO_2 , NH_2 , NHC_{1-4} alkyl, or C_{1-4} alkylCO— ; or a pharmaceutically acceptable salt thereof.

This invention further relates to pharmaceutical compositions comprising a nontoxic effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

This invention also relates to pharmaceutical compositions for inhibiting antigen-induced respiratory anaphylaxis comprising a nontoxic effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, an histamine H_1 -receptor antagonist, and a pharmaceutically acceptable carrier or diluent.

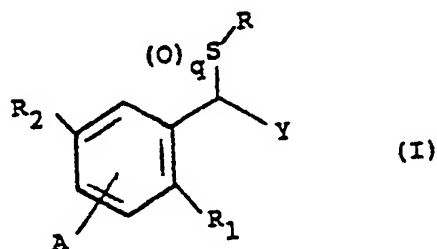
This invention also relates to a method of treating diseases in which leukotrienes are a factor in a subject in need thereof comprising administering to such subject a nontoxic effective amount of one of the above described pharmaceutical compositions.

This invention also relates to a process for preparation of the compounds of Formula (I) of known chirality comprising a) reacting an appropriate diester with a strong base to generate an intermediate thiol, and b) react-

ing the thiol with an alkylating agent or Michael acceptor, i.e., α , β unsaturated carbonyl compound to yield a compound of Formula (I).

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds represented by structural formula (I)



wherein

q is 0, 1, or 2 ;

R₁ is (L)_a-(CH₂)_b-(T)_c-M

a is 0 or 1 ;

b is 3 to 14 ;

c is 0 or 1 ;

L and T are independently sulfur, oxygen, or CH₂ with the proviso that L and T are not sulfur when q is 1 or 2 ; and

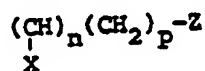
M is C₁₋₄ alkyl, ethynyl, trifluoromethyl, isopropenyl, furanyl, thienyl, cyclohexyl or phenyl optionally mono-substituted with Br, Cl, CF₃, C₁₋₄ alkoxy, C₁₋₄ alkyl, methylthio, or trifluoromethylthio ;

R₂ and A are independently selected from H, CF₃, C₁₋₄ alkyl, C₁₋₄ alkoxy, F, Cl, Br, I, OH, NO₂ or NH₂ ;

or R₁ and A are H and

R₂ is (L)_a-(CH₂)_b-(T)_c-M wherein a, b, c, L, T, and M are as defined above ;

Y is COR₃ or



wherein

R₃ is OH, NH₂, aryloxy, or C₁₋₆ alkoxy ;

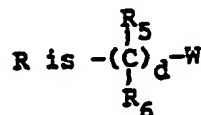
n is 0 or 1 ;

p is 0, 1 or 2 ;

X is H, OH, C₁₋₄ alkyl, C₁₋₄ alkoxy,

or F ; and

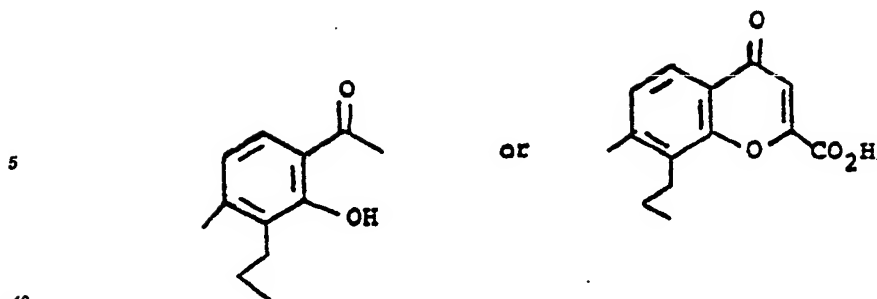
Z is COR₃ or tetrazolyl ;



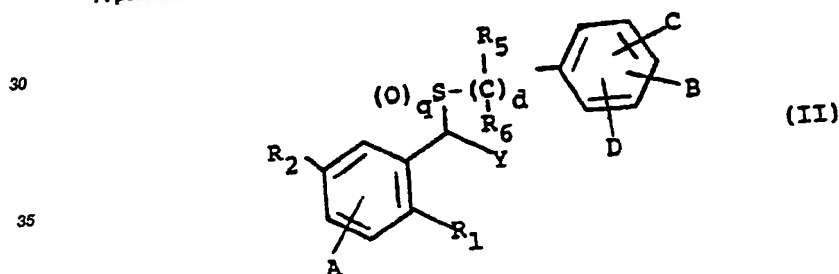
R₅ and R₆ are each hydrogen or C₁₋₄ alkyl at any point when d is not 0 ;

d is 0 to 6 ;

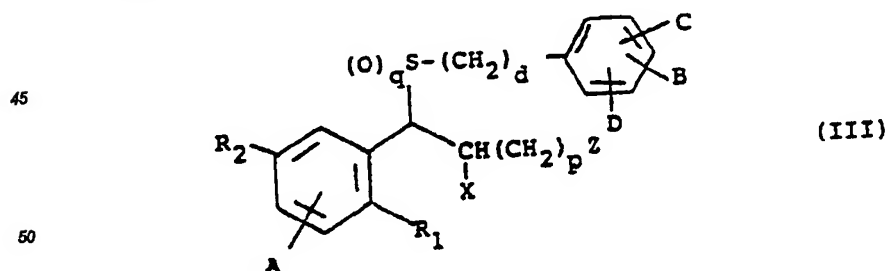
W is a six-membered aryl or heteroaryl ring selected from phenyl, pyridyl, or pyrimidyl, unsubstituted or substituted by one or more of B, C, or D, or W is one of



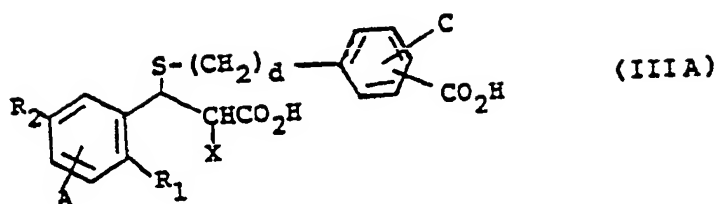
20 wherein
 R_5 and R_6 are each hydrogen or C_{1-4} alkyl ;
 p is 0 to 6 ;
 V is H, C_{1-4} alkyl, COR_3 , SO_3H , SO_2H , SO_2NH_2 , $COCH_2OH$, $CHOHCH_2OH$, or tetrazolyl, with R_3 as defined
 above ;
 C and D are independently selected from H, OH, F, Cl, Br, CF_3 , C_{1-4} alkyl, C_{1-4} alkoxy, methylthio, trif-
 25 luoromethylthio, NO_2 , NH_2 , NHC_{1-4} alkyl, or C_{1-4} alkylCO— ;
 or a pharmaceutically acceptable salt thereof.
 A particular class of compounds of this invention are those represented by structural formula (II)



40 wherein R_1 , R_2 , A, B, C, D, R_5 , R_6 , q, d and Y are as defined above.
 A subgeneric class of these compounds are those represented by structural formula (III)



55 wherein X, Z, R_1 , R_2 , A, B, C, D, q, p, and d are as defined above.
 A particular group of the subgeneric class represented by formula (III) are the compounds represented by
 structural formula (IIIA)



10 wherein

X is OH, H, or OCH₃;

d is 0 or 1; and

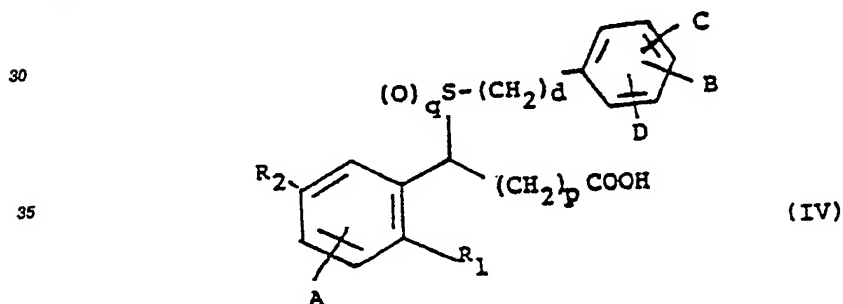
R₁, R₂, A, and C are as defined above.

The compounds of formulae (III) and (III A) are exemplified by the following compounds:

- 15 (1) 2-Hydroxy-3-(2-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 (2) 2(S)-Hydroxy-3(R)-(2-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 (3) 2(S)-Hydroxy-3(R)-(3-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 (4) 2-Hydroxy-3-(3-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 (5) 2-Hydroxy-3-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 20 (6) 2-Hydroxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 (7) 2-Hydroxy-3-(4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 (8) 2-Hydroxy-3-(2-fluoro-4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 (9) 2-Methoxy-3-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid; and
 (10) 2-Hydroxy-3-(4-hydroxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.
 25 (11) 2-Methoxy-3-[4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

A second subgeneric class of the compounds of formula (II) are those represented by structural formula

(IV)



40 wherein R₁, R₂, A, B, C, D, q, and d are as defined above and p is 1 or 2.

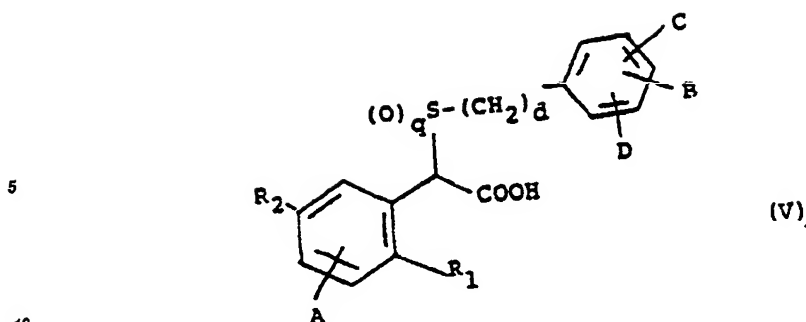
The compounds of formula (IV) are exemplified by the following compounds:

- 45 (1) 3-(2-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 (2) 3-(2-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid; and
 (3) 3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

A third subgeneric class of the compounds of formula (II) are those represented by structural formula (V)

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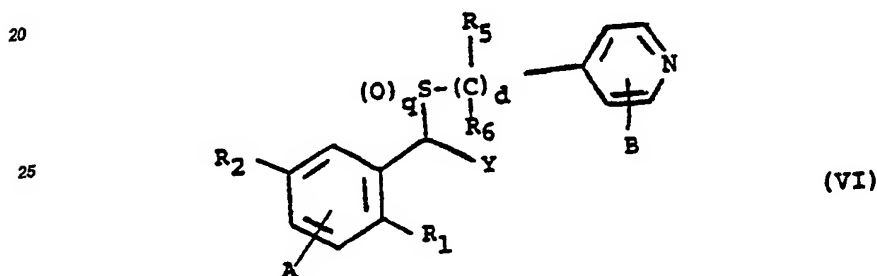


wherein R_1 , R_2 , A, B, C, D, q, and d are as defined above.

The compounds of formula (V) are exemplified by the following compounds:

- 15
- (1) 2-(2-carboxyphenylthio)-2-[2-(8-phenyloctyl) phenyl]acetic acid;
 - (2) 2-(2-carboxyphenylmethylthio)-2-[2-(8-phenyloctyl)phenyl]acetic acid;
 - (3) 2-(3-carboxyphenylmethylthio)-2-[2-(8-phenyloctyl)phenyl]acetic acid;

A further particular class of compounds of this invention are those represented by structural formula (VI)



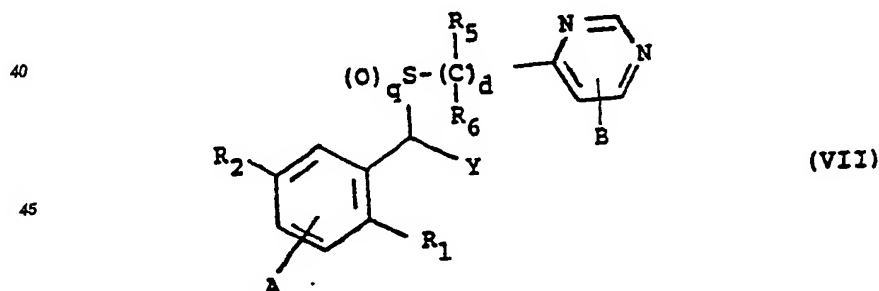
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wherein R_1 , R_2 , A, B, Y, R_5 , R_6 , q, and d are as defined above for formula (I).

The compounds of formula (VI) are exemplified by the following compounds:

- 35
- (1) 2-Hydroxy-3-(2-carboxy-4-pyridylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 - (2) 3-(2-carboxy-4-pyridylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid; and
 - (3) 2-(3-carboxy-4-pyridylmethylthio)-2-[2-(8-phenyloctyl)phenyl]acetic acid;

A further particular class of compounds of this invention are those represented by structural formula (VII)



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wherein R_1 , R_2 , A, B, R_5 , R_6 , Y, q, and d are as defined above.

The compounds of formula (VII) are exemplified by the following compounds:

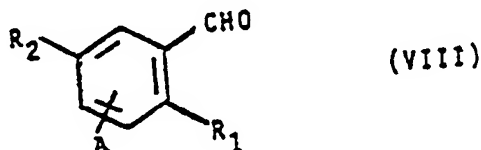
- 55
- (1) 2-Hydroxy-3-(2-carboxy-4-pyrimidylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 - (2) 3-(2-carboxy-4-pyrimidylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid; and
 - (3) 2-(2-carboxy-4-pyrimidylmethylthio)-2-[2-(8-phenyloctyl)phenyl]acetic acid;

The compounds of the present invention, which contain one or two carboxylic acid groups, are capable of forming salts with pharmaceutically acceptable bases, according to procedures well known in the art. Such acceptable bases include organic and inorganic bases, such as ammonia, arginine, organic amines, alkaline

earth and alkali metal bases. Of particular utility are the potassium, sodium, ammonium, magnesium and calcium salts.

Some of the compounds of formula (I) contain one or two asymmetric centers. This leads to the possibility of two or four stereoisomers for each such compound. The present invention includes all such stereoisomers, racemates, or mixtures thereof.

The compounds of the formula (I) wherein Y is CO₂H are conveniently prepared from an aldehyde precursor of the following structural formula (VIII)



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wherein R₁ and R₂ are described above. A compound of formula (VIII) is treated with trimethylsilyl cyanide in the presence of zinc iodide at low temperatures in an inert solvent to form the trimethylsilyl-protected cyanohydrin. Treatment of this with gaseous hydrogen chloride in methanol provides the methyl 2-hydroxyacetate derivative which is converted to the 2-chloroacetate with thionyl chloride. This valuable intermediate is then reacted with a substituted thiol selected to give, after removal of ester protective groups, a product of formula (I).

20

The compounds of the formula (I) wherein Y is CH₂CO₂H or CH(X)CO₂H wherein X is H, C₁₋₄ alkyl, or C₁₋₄ alkoxy are prepared by reacting the appropriate aldehyde of the formula (VIII) and an esterified bromoacetate, conveniently t-butyl bromoacetate, with a mixture of diethyl aluminum chloride, zinc dust and a catalytic amount of cuprous bromide at low temperatures in an inert solvent to give the esterified 3-hydroxypropionate derivative

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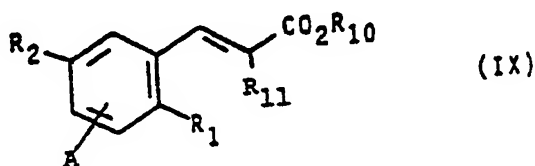
which is reacted directly with a substituted thiol in trifluoroacetic acid. Alternatively, a mixture of trimethyl borate and zinc in tetrahydrofuran may be used to prepare the 3-hydroxypropionate derivative. Alternatively an aldehyde of formula (VIII) may be reacted at low temperature with the lithium salt of an esterified acetic acid, conveniently t-butylacetate, in an inert solvent to give the esterified 3-hydroxypropionate derivative. By employing an esterified 2-bromopropionate in the above reaction with an aldehyde (VIII), the compounds of the formula

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(I) wherein Y is CH(CH₃)CO₂H are obtained.

To prepare the compounds of formula (I) wherein q is 1 or 2, the appropriate thio product is conveniently oxidized with sodium periodate or meta-chloroperoxybenzoic acid to obtain the sulfoxide or sulfone product.

Alternatively, the compounds of the formula (I) wherein Y is CH(X)CO₂H wherein X is H, C₁₋₄ alkyl, C₁₋₄ alkoxy, or fluoro are prepared from a propenoate precursor of the following structural formula (IX)



45

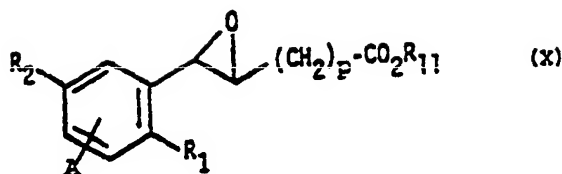
wherein R₁ and R₂ are described above, R₁₀ is a standard ester protective group, such as t-butyl, and R₁₁ is H, C₁₋₄ alkyl, C₁₋₄ alkoxy, or fluoro. A compound of formula (IX) is reacted with a mixture of alkali metal alkoxide, such as sodium methoxide, and substituted thiol to give, after removal of the ester protective group, products of formula (I).

The propenoate precursors of formula (IX) are prepared from the corresponding aldehydes of formula (VIII) by general procedures such as reaction with an alkyl (triphenylphosphoranylidene)acetate or by conversion of the aldehyde to a 3-hydroxypropionate derivative, as described above, followed by an elimination reaction to form the double bond. Additionally, the propenoate precursor is obtained from a 3-methanesulfonyloxypropionate derivative by treatment with triethylamine.

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The compounds of the formula (I) wherein Y is CH(OH)(CH₂)_pCO₂H are prepared from an epoxide precursor of the following structural formula (X)

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10 wherein R_1 , R_2 , A and p are described above, and R_{11} is lower alkyl, such as methyl or ethyl. A compound of formula (X) is reacted in an aprotic solvent with triethylamine and a substituted thiol selected to give, after removal of ester protective groups, a product of formula (I).

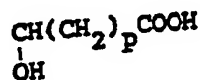
The epoxide precursors of formula (X) where p is 2 are prepared by reaction of the Grignard derivative of a bromobenzene compound of the formula (XI)



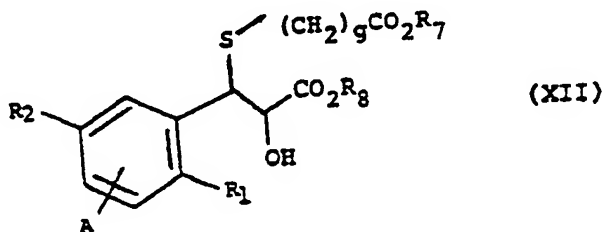
20 with acrolein to give the corresponding enol derivative which is treated with a trialkylorthoacetate, followed by epoxidation using m-chloroperbenzoic acid.

25 The epoxide precursors of formula (X) where p is 0 are prepared by reaction of an aldehyde of the formula (VIII) with a lower alkyl chloroacetate and an alkali metal alkoxide, such as sodium methoxide.

The compounds for formula (I) wherein Y is



can also be prepared from an ester of the following structural formula (XII)

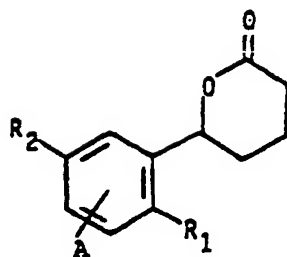


40 wherein R_7 and R_8 are the same or different and are C_{1-6} alkyl, and g is 2. A compound of formula (XII) is reacted with sodium hydride in an inert solvent followed by reaction with a substituted benzyl bromide to yield a product of formula (I).

45 The compounds of the formula (I) wherein Y is $(\text{CH}_2)_3\text{CO}_2\text{H}$ are prepared from a tetrahydro-4H-pyran-2-one precursor of the following structural formula (XIII)

50

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(XIII)

wherein R_1 and R_2 are described above. A compound of formula (XIII) is reacted with a mixture of zinc iodide and a substituted thiol in an inert solvent or with a substituted thiol in trifluoroacetic acid to give, after removal of any ester protective group, a product of formula (I).

The tetrahydro-4H-pyran-2-one precursors of formula (XIII) are prepared by reaction of the Grignard derivative of the bromobenzene compound of formula (XI) with chloro titanium tri-isopropoxide followed by reaction with 5-oxovalerate alkyl ester.

The aldehydes of the formula (VIII) are known or readily prepared utilizing the general procedures described as follows.

The aldehyde precursors to the compounds of the formula (I) wherein R_1 is, for example, an alkyl radical containing 8 to 13 carbon atoms are prepared from the appropriate 2-alkoxyphenyl-4,4-dimethyloxazoline [see Meyers et al. *J. Org. Chem.*, 43 1372 (1978)].

The aldehyde precursors of the compounds of the formula (I) wherein R_1 is, for example, an alkoxy radical containing 7 to 12 carbon atoms are prepared by the O-alkylation of the appropriate 2-hydroxybenzaldehyde with the corresponding alkylating agent.

The aldehyde precursors to the compounds of the formula (I) wherein R_1 is a 1-alkynyl radical containing 10 to 12 carbon atoms are prepared by coupling a 2-halobenzaldehyde with the appropriate 1-alkyne in the presence of cuprous iodide and $(\text{Ph}_3)_2\text{PdCl}_2$. [See Hagihara, et al. *Synthesis*, 627, (1980)]. The catalytic hydrogenation of these alkynyl containing precursors under standard conditions affords the aldehyde precursors of the compounds of the formula (I) wherein R_1 is an alkyl or phenylalkyl radical.

The alkylthio containing aldehyde precursors of the compounds of the formula (I) are prepared by the reaction of the appropriately substituted o-haloalkylthiobenzene with magnesium and dimethylformamide.

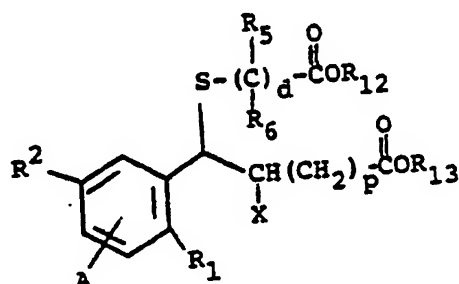
The phenylthioalkyl containing aldehyde precursors of the compounds of the formula (I) are prepared by the reaction of the appropriately substituted haloalkyl benzaldehyde with a thiophenol and triethylamine.

The heteroaryl mercaptan precursors necessary to prepare the compounds of formula (I) are known compounds and are conveniently prepared employing standard chemical reactions. The mercapto derivatives of these precursors are prepared according to known methods. These mercaptans are reacted as described above to yield compounds of formula (I).

Appropriate modifications of the general processes disclosed, and as further described in the Examples provided hereinbelow, furnish the various compounds defined by formula (I).

This invention further relates to a process for the preparation of the compounds of Formula (I) of known chirality comprising reacting a diester with a strong base to generate a thiol which is then reacted with an alkylating agent or Michael acceptor to yield the desired compound.

An appropriate diester is represented by Formula (XIV)



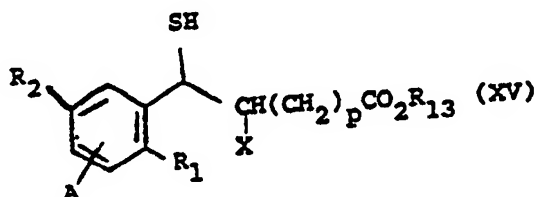
(XIV)

wherein

d is 2 ;

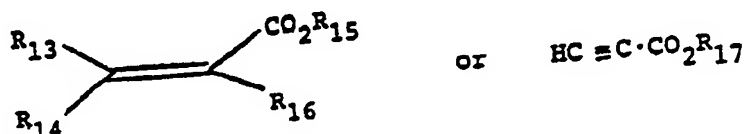
X is OH ;

one of R₅ or R₆ adjacent to the ester group is H and the other is H or C₁₋₄ alkyl ; and
 R₁, R₂, A, and p are as defined in Formula (I) and R₁₂ and R₁₃ are independently selected from C₁₋₆ alkyl.
 Suitable strong bases include those such as sodium methoxide, sodium hydride, sodium amide, lithium
 diisopropyl amide or others. The reaction is conducted in an aprotic solvent such as tetrahydrofuran,
 dimethylsulfoxide, or N,N-dimethylformamide at ambient temperature and pressure. The resulting inter-
 mediate thiol of known chirality is represented by Formula (XV)



wherein

R₁, R₂, R₁₃, A, X, and p are as defined in Formula (XIV).
 The thiol of Formula (XV) is reacted with an alkylating agent or Michael acceptor to yield a compound of
 Formula (I). Suitable alkylating agents include alkyl halides such as alkyl bromide or alkyl iodide. Benzyl halides
 are especially suitable to prepare compounds of Formula (I). The reaction is conducted in an aprotic solvent
 at ambient temperature and pressure. Suitable Michael acceptors include compounds which undergo nuc-
 leophilic addition. Examples include compounds containing carbonyl, carboalkoxy, or cyano groups conjugated
 with a double or triple bond. Carbonyl compounds or alkynes represented by the following structural formulae
 are especially suitable



wherein R₁₃, R₁₄, and R₁₆ are independently selected from hydrogen or C₁₋₆ alkyl. R₁₅ and R₁₇ are independently
 selected from H, aryl, or C₁₋₆ alkyl. The reaction is conducted in an aprotic solvent at ambient temperature and
 pressure.

The leukotriene antagonist activity of the compounds of this invention is measured by the ability of the com-
 pounds to inhibit the leukotriene induced contraction of guinea pig tracheal tissues in vitro. The following meth-
 odology was employed :

In vitro : Guinea pig (adult male albino Hartley strain) tracheal spiral strips of approximate dimensions 2 to
 3 mm cross-sectional width and 3.5 cm length were bathed in modified Krebs buffer in jacketed 10 ml tissue
 bath and continuously aerated with 95% O₂/5% CO₂. The tissues were connected via silk suture to force dis-
 placement transducers for recording isometric tension. The tissues were equilibrated for 1 hr., pretreated for
 15 minutes with meclofenamic acid (1μM) to remove intrinsic prostaglandin responses, and then pretreated for
 an additional 30 minutes with either the test compound or vehicle control. A cumulative concentration-response
 curve for LTD₄ on triplicate tissues was generated by successive increases in the bath concentration of the
 LTD₄. In order to minimize intertissue variability, the contractions elicited by LTD₄ were standardized as a per-
 centage of the maximum response obtained to a reference agonist, carbachol (10μM).

Calculations : The averages of the triplicate LTD₄ concentration-response curves both in the presence and
 absence of the test compound were plotted on log graph paper. The concentration of LTD₄ needed to elicit 30%
 of the contraction elicited by carbachol was measured and defined as the EC₃₀. The -log K_B value for the test
 compound was determined by the following equations :

$$1. \frac{EC_{30} \text{ (presence of test compound)}}{EC_{30} \text{ (presence of vehicle control)}} = \text{dose ratio} = X$$

$$2. K_B = \text{concentration of test compound}/(X-1)$$

The compounds of this invention possess biosignificant antagonist activity against leukotrienes, primarily leukotriene D₄. The antagonist activity of representative compounds of this invention is listed in Table I. The -log K_B values were calculated from the above protocol. Where compounds were tested more than once, the -log K_B values given here represent the current average data.

Table I

Leukotriene Antagonist Activity

Compounds of Formula (III) wherein R₂, A, C, and D are hydrogen, q is O, p is O, Z is CO₂H, and R₁ is 8-phenyloctyl

8-phenyloctyl				In Vitro
	<u>d</u>	<u>B</u>	<u>X</u>	<u>-Log K_B</u>
25				5.5
	1)	0	2-CO ₂ H	OH
	2)	1	2-CO ₂ H	OH
	3)	1	3-CO ₂ H	OH
30	4)	0	3-CO ₂ H	OH
	5)	0	4-CO ₂ H	OH
	6)	1	2-OCH ₃ ,	OH
35			4-CO ₂ H	
	7)	1	4-CO ₂ H	OH
	8)	1	2-F,	
40			4-CO ₂ H	OH
	9)	0	4-CO ₂ H	OCH ₃
	10)	0	4-OH	OH
	11)	1	4-CO ₂ H	OCH ₃
45			2-OCH ₃	
	12)	1	4-CO ₂ H	H
			2-OCH ₃	
50	13)	1	2-OCH ₃	OH
			5-CO ₂ H	

Pharmaceutical compositions of the present invention comprise a pharmaceutical carrier or diluent and an amount of a compound of the formula (I) or a pharmaceutically acceptable salt, such as an alkali metal salt thereof, sufficient to produce the inhibition of the effects of leukotrienes, such as symptoms of asthma and other hypersensitivity diseases.

When the pharmaceutical composition is employed in the form of a solution or suspension, examples of appropriate pharmaceutical carriers or diluents include : for aqueous systems, water ; for non-aqueous systems, ethanol, glycerin, propylene glycol, corn oil, cottonseed oil, peanut oil, sesame oil, liquid paraffins and mixtures thereof with water ; for solid systems, lactose, kaolin and mannitol ; and for aerosol systems, 5 dichlorodifluoromethane, chlorotrifluoroethane and compressed carbon dioxide. Also, in addition to the pharmaceutical carrier or diluent, the instant compositions may include other ingredients such as stabilizers, anti-oxidants, preservatives, lubricants, suspending agents, viscosity modifiers and the like, provided that the additional ingredients do not have a detrimental effect on the therapeutic action of the instant compositions.

The nature of the composition and the pharmaceutical carrier or diluent will, of course, depend upon the intended route of administration, i.e. parenterally, topically or by inhalation. 10 In general, particularly for the prophylactic treatment of asthma, the compositions will be in a form suitable for administration by inhalation. Thus the compositions will comprise a suspension or solution of the active ingredient in water for administration by means of a conventional nebulizer. Alternatively the compositions will comprise a suspension or solution of the active ingredient in a conventional liquified propellant or compressed 15 gas to be administered from a pressurized aerosol container. The composition may also comprise the solid active ingredient diluted with a solid diluent for administration from a powder inhalation device. In the above compositions, the amount of carrier or diluent will vary but preferably will be the major proportion of a suspension or solution of the active ingredient. When the diluent is a solid it may be present in lesser, equal or greater amounts than the solid active ingredient.

For parenteral administration the pharmaceutical composition will be in the form of a sterile injectable solution or an aqueous or nonaqueous liquid suspension. 20

For topical administration the pharmaceutical composition will be in the form of a cream or ointment. Usually a compound of formula I is administered to an animal subject in a composition comprising a non-toxic amount sufficient to produce an inhibition of the symptoms of an allergic response. When employed in 25 this manner, the dosage of the composition is selected from the range of from 350 mg. to 700 mg. of active ingredient for each administration. For convenience, equal doses will be administered 1 to 4 times daily with the daily dosage regimen being selected from about 350 mg. to about 2800 mg.

The pharmaceutical preparations thus described are made following the conventional techniques of the pharmaceutical chemist as appropriate to the desired end product. 30

Included within the scope of this disclosure is the method of inhibiting the symptoms of an allergic response resulting from a mediator release which comprises administering to an animal subject a therapeutically effective amount for producing said inhibition of a compound of formula I, preferably in the form of a pharmaceutical composition. The administration may be carried out in dosage units at suitable intervals or in single doses as 35 needed. Usually this method will be practiced when relief of allergic symptoms is specifically required. However, the method is also usefully carried out as continuous or prophylactic treatment. It is within the skill of the art to determine by routine experimentation the effective dosage to be administered from the dose range set forth above, taking into consideration such factors as the degree of severity of the allergic condition being treated, and so forth.

Compounds of this invention, alone and in combination with a histamine H_1 -receptor antagonist, inhibit antigen-induced contraction of isolated, sensitized guinea pig trachea (a model of respiratory anaphylaxis). Exemplary of histamine H_1 -receptor antagonists are mepyramine, chlorpheniramine, and 2-[4-(5-bromo-3-methyl-pyrid-2-yl)butylamino]-5-[(6-methyl-pyrid-3-yl)methyl]-4-pyrimidone, and other known 40 H_1 -receptor antagonists.

Pharmaceutical compositions, as described hereinabove, of the present invention also comprise a pharmaceutical carrier or diluent and a combination of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, and an histamine H_1 -receptor antagonist in amounts sufficient to inhibit antigen-induced 45 respiratory anaphylaxis. The above-defined dosage of a compound of formula I is conveniently employed for this purpose and the known effective dosage for the histamine H_1 -receptor antagonist. The methods of administration described above for the single active ingredient can similarly be employed for the combination with a histamine H_1 -receptor antagonist. 50

The following examples illustrate the preparation of the compounds of this invention and their incorporation into pharmaceutical compositions and as such are not to be considered as limiting the invention set forth in the claims appended hereto.

EXAMPLE 1**Preparation of 2-Hydroxy-3-(2-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid****(a) 2-(8-Phenyloctyl)benzaldehyde**

A solution of 8-phenyloctanoic acid (19.8 mmol) in sieve dried tetrahydrofuran (5 ml) was reduced with diborane in tetrahydrofuran (30 ml, 29.1 mmol) at 0°C for 4 hours to give 8-phenyloctanol. To an ice cold solution of the octanol (ca. 19.8 mmol) and carbon tetrabromide (21.98 mmol) in methylene chloride (50 ml) was added triphenylphosphine (22.30 mmol) in methylene chloride (50 ml) and the resulting solution was stirred for 2.5 hours. The volatiles were evaporated and the residue was taken up in ether (100 ml), cooled in ice, and filtered. The filtrate was evaporated and distilled to afford 8-phenyloctyl bromide as an oil.

To 8-phenyloctylmagnesium bromide (from 24.25 mmol of 8-phenyloctyl bromide and 21.27 mmol of magnesium) in distilled tetrahydrofuran (40 ml) was added 2-(2-methoxyphenyl)-4, 4-dimethyloxazoline (17.10 mmol) [A.I. Meyers et al., *J. Org. Chem.*, 43, 1372 (1978)] in tetrahydrofuran (20 ml). After stirring for 24 hours, the reaction mixture was worked up to yield 2-[2-(8-phenyloctyl)phenyl]-4,4-dimethyloxazoline as an oil. A solution of the oxazoline (11.58 mmol) in methyl iodide (20 ml) was refluxed under argon for 18 hours. Removal of the volatiles afforded the corresponding 3,4,4-trimethyloxazolinium iodide as a white solid (mp 76.5-78°C).

To an ice cold solution of the iodide (9.46 mmol) in methanol (35 ml) was added in portions sodium borohydride (9.20 mmol). The reaction mixture was allowed to stir for 30 minutes and was then quenched with 5 percent sodium hydroxide (50 ml). The reaction mixture was extracted with diethyl ether (2 x 50 ml) and the extract was washed with brine (50 ml) and dried over anhydrous magnesium sulfate and filtered. Evaporation of the filtrate afforded an oil which was dissolved in acetone (50 ml) and 3N hydrochloric acid (10 ml) was added. The mixture was flushed with argon and stirred for 16 hours at ambient temperature. The volatiles were removed under vacuum and the residue partitioned between diethyl ether (50 ml) and water (50 ml). The aqueous phase was extracted with more diethyl ether (50 ml). The combined organic phase was washed with brine (50 ml) and dried over anhydrous magnesium sulfate. Evaporation of the organic phase yielded an oil which was purified by flash chromatography over silica gel with 2 percent ethyl acetate in hexane as eluant to afford the desired product as a colorless oil.

Analysis for $C_{21}H_{28}O$: Calculated: C, 85.67; H, 8.90. Found: C, 85.12, 85.22; H, 8.94, 8.96.

(b) Alternative preparation of 2-(8-phenyloctyl)benzaldehyde

A solution of 5-hexynyl alcohol (102 mmol) in pyridine (150 ml), under argon, was cooled to 0°C and p-toluenesulfonyl chloride (204 mmol) was added. The reaction mixture was kept at about 4°C for 18 hours, poured into ice-water and then taken up in ether. The ether extract was washed with cold 10% hydrochloric acid, water and brine. The organic layer was dried and concentrated *in vacuo* to give 5-hexynyl p-toluenesulfonate. A solution of phenylacetylene (97 mmol) in tetrahydrofuran (200 ml) containing a trace of triphenylmethane was cooled to 0°C and then n-butyl lithium (37.3 ml of 2.6 mol in hexane) was added dropwise. The resulting solution was stirred at 0°C for 10 minutes and hexamethylphosphoramide (21 ml) was added dropwise. After stirring for 10 minutes a solution of 5-hexynyl p-toluenesulfonate (97.1 mmol) in tetrahydrofuran (200 ml) was added. The reaction mixture was stirred at room temperature for 18 hours, diluted with ether and the organic layer was washed with water and brine. The dried organic solution was concentrated and the product was purified by flash chromatography to give 1-phenylocta-1,7-diyne. A mixture of this compound (43 mmol), 2-bromobenzaldehyde (35.8 mmol), cuprous iodide (0.5 mmol) and bis(triphenylphosphine) palladium (II) chloride (0.7 mmol) in triethylamine (100 ml) was heated in an oil bath (95°C) for one hour. The reaction mixture was cooled to 0°C, filtered and the filtrate was concentrated. The residue was dissolved in ether, washed with 10% hydrochloric acid, water and brine. The organic layer was dried and concentrated to give a product which was purified by flash chromatography to yield 2-(8-phenyl-1,7-octadienyl)benzaldehyde. A solution of this compound (24.1 mmol) in ethyl acetate (100 ml) and 10% palladium on charcoal (1 g) was hydrogenated (40 psi of hydrogen) at room temperature for 15 minutes. The catalyst was filtered off and the filtrate concentrated to give the 2-(8-phenyloctyl)benzaldehyde.

(c) Methyl trans-3-[2-(8-Phenyloctyl)phenyl]-2,3-epoxypropionate

The compound of Example 1(a) or (b) (2.94 g, 10 mmol) was dissolved in diethyl ether (25 ml) and the solution was stirred under argon at 0°C. Methyl chloroacetate (1.32 ml, 15 mmol) was added, followed by the addition of sodium methoxide (810 mg, 15 mmol). The mixture was stirred for 2.5 hours at ice bath temperature. A

small quantity of water was added, the ether phase separated, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was flash chromatographed on 80 grams of silica gel eluted with 5-30% ethyl acetate/hexane to give the product.

5 (d) Methyl 2-hydroxy-3-(2-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionate

A solution of the compound of Example 1(c) (0.51 gm, 1.39 mmol), 2-mercaptobenzoic acid (0.24 gm, 1.53 mmole) and triethylamine (0.31 g, 3.06 mmol) in 10 ml of methanol were stirred overnight at 22° under argon. The mixture was poured into water, acidified with 1N hydrochloric acid, and extracted with diethylether. The extracts were dried and the solvent evaporated. The residue was chromatographed on silica gel to remove starting materials and the product eluted with a mixture of ethyl acetate, hexane and methanol (60 : 40 : 2.5). The solvents were evaporated, and the residue recrystallized from methanol, to yield the product, 230 mg (32%).

10 (e) 2-Hydroxy-3-(2-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

15 A suspension of the compound of Example 1(d) (0.23 gm, 0.44 mmol), 5 ml of methanol, 2 ml of water and 2 ml of 2.5N sodium hydroxide was heated at 95° for 10 minutes, and stirred at 22° for 2 hr. The mixture was diluted with 20 ml of water, and filtered. The filtrate was acidified, and extracted with ethyl acetate. The extracts were washed with water, dried, and the solvent evaporated. The residue was recrystallized from acetonitrile and gave the desired product, 182 mg (82%).

20 nmr (CDCl₃/Me₂CO) 9.70 ppm (broad s, 3H), 7.05-8.06 (m, 13H), 5.28 (d, 1H), 4.76 (d, 1H), 2.40-3.05 (m, 4H), 1.13-1.72 (m, 12H).

Similarly, the following compounds are prepared according to the general method of example 1 from the 2-(2-methoxyphenyl)-4,4-dimethyloxazoline and the appropriate alkyl halide :

- 25 2-Hydroxy-3-(2-carboxyphenylthio)-3-[2-(3-phenylpropyl)phenyl]propionic acid ;
2-Hydroxy-3-(2-carboxyphenylthio)-3-[2-(14-phenyltetradecyl)phenyl]propionic acid ;
2-Hydroxy-3-(2-carboxyphenylthio)-3-(2-butylphenyl)propionic acid ;
2-Hydroxy-3-(2-carboxyphenylthio)-3-(2-dodecylphenyl)propionic acid ; and
2-Hydroxy-3-(2-carboxyphenylthio)-3-(2-octadecyl)propionic acid.

30

EXAMPLE 2

Preparation of 2(S)-Hydroxy-3(R)-(2-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

35 (a) Methyl 3-(2-Carbomethoxyethylthio)-3-[2-(8-phenyloctyl)phenyl]-2-hydroxypropionate

The compound of Example 1(c) (1.2 g, 3.28 mmol) was dissolved in methanol (20 ml) containing 2% triethylamine and stirred under argon at room temperature. Methyl 3-mercaptoacetate (0.623 ml, 5.45 mmole) and triethylamine (1.45 ml, 9.84 mmol) were dissolved in methanol (15 ml) and added dropwise. The mixture was stirred for 18 hours. The solvent was stripped and the residue eluted with 20% ethyl acetate/hexane to give a mixture of the desired product and its regioisomer, methyl 2-(2-carbomethoxyethylthio)-3-[2-(8-phenyloctyl)phenyl]-3-hydroxypropionate. The mixture was rechromatographed on 100 g of neutral alumina to separate the desired product.

40 (b) Erythro-3-(2-carboxyethylthio)-3-[2-(8-phenyloctyl)phenyl]-2-hydroxypropionic acid

45 The desired product of Example 2(a) (320 mg, 0.66 mmol) was dissolved in methanol (10 ml) and stirred under argon at ice bath temperature. A 1N solution of sodium hydroxide (2.5 ml, 2.5 mmol) was added dropwise, the ice bath removed, the mixture stirred at room temperature for 2.5 hours, and then cooled for 18 hours. After an additional 1 hours of stripping at room temperature, the methanol was stripped, the residue diluted with water and the pH adjusted to 3.5 with dilute hydrochloric acid. Extraction with ethyl acetate followed by drying over anhydrous sodium sulfate, filtration and evaporation gave the crude product which was flash chromatographed on 20 grams of silica gel eluted with 30 : 70 : 0.5 ethyl acetate : hexane : formic acid to give the free acid product.

50 (c) Resolution of 3-(2-carboxyethylthio)-3-[2-(8-phenyloctyl)phenyl]-2-hydroxypropionic acid

55 The racemic diacid of Example 2(b) (63.5 g, 0.138 mol) in 700 ml of isopropanol was treated with a solution of (R)-4-bromo- α -phenethylamine (57.1 g, 0.286 mol) in 200 ml of isopropanol at 25°C. The resulting solution

was stirred for 3 hours, causing crystallization of the 2S, 3R diamine salt. The suspension was cooled to 5°C, filtered, and the salt recrystallized twice from ethanol to give 37.7 g (72%) of 2S, 3R diamine salt, m.p. 146-147°C; $[\alpha]_D^{24} = -15.8^\circ$ (C = 1, CH₃OH).

The diamine salt (37.7 g, 0.0497 mol) was added in portions to 400 ml of cold 0.5N aqueous hydrochloric acid. The mixture was extracted with ethyl acetate, and the ethyl acetate solution washed three times with 0.5N hydrochloric acid. The ethyl acetate solution was washed with saturated sodium chloride solution, dried, and concentrated to give 19.5 g (97%) of the desired 2(S)-hydroxy-3(R)-(2-carboxyethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid; $[\alpha]_D^{24} = -40.8^\circ$ (C = 1, CHCl₃).

(d) Methyl 2(S)-hydroxy-3(R)-(2-carbomethoxyethylthio)-3-[2-(8-phenyloctyl)phenyl] propionate

A solution of 2(S)-hydroxy-3(R)-(2-carboxyethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid (1.0 g, 2.18 mmol) in 100 ml of diethylether was treated with an ethereal solution of diazomethane for 30 minutes at room temperature. Evaporation of the ether gave methyl-2(S)-hydroxy-3(R)-(2-carbomethoxyethylthio)-3-[2-(8-phenyloctyl)phenyl]propionate, 1.06 g (100%).

(e) Methyl 2(S)-Hydroxy-3(R)-(carbomethoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionate

A solution of the compound of Example 2(d) (675 mg, 1.39 mmol) in 12 ml of tetrahydrofuran and 4 ml of N,N-dimethylformamide at 0° was treated with sodium hydride (2.92 mmol). After 30 min, 2-carbomethoxybenzyl bromide (350 mg, 1.53 mmol) was added and the mixture stirred at 22° for 2 hours and 60° for 2 hours. After cooling, the mixture was diluted with water, acidified, and extracted with ethyl acetate. The extracts were dried and the solvent evaporated. The residue was chromatographed first over silica gel with ethyl acetate/hexane (3 : 7) as eluant, then over an alumina column with ethyl acetate/hexane/methanol (75 : 25 : 1) as eluant. The product was isolated as an oil, 230 mg.

(f) 2(S)-Hydroxy-3(R)-(3-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

A solution of the compound of Example 2(e) (130 mg, 0.24 mmol) in 2 ml of methanol was treated with 2 ml of 2.5N sodium hydroxide, and heated at 80° for 10 minutes. The solution was diluted with 10 ml of water, filtered, the filtrate acidified and extracted with ethyl acetate. The extracts were washed with water, dried and the solvent removed to yield the product as an oil, 97 mg (78%). nmr (CDCl₃/Me₂CO) 8.05 ppm (d, 1H), 7.67 (m, 1H), 6.96-7.47 (m, 11H), 4.78 (d, 1H), 4.58 (d, 1H), 4.39 (d, 1H), 4.18 (d, 1H), 2.20-2.72 (m, 4H), 1.06-1.72 (m, 12H).

EXAMPLE 3

Preparation of 2(S)-Hydroxy-3(R)-(3-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

(a) Methyl 2(S)-hydroxy-3(R)-(3-carboethoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionate

A solution of the compound of Example 2(d) (370 mg, 0.76 mmol) in 10 ml of tetrahydrofuran and 5 ml of N,N-dimethylformamide was treated first with sodium hydride (1.53 mmol) followed by 3-carboethoxybenzyl bromide (203 mg, 0.84 mmol). The mixture was stirred at 22° for 1 hr, poured into 100 ml of cold 0.1N hydrochloric acid, and extracted with diethyl ether. The extracts were washed with water, dried, and the drying agent filtered. The filtrate was treated with an ethereal solution of diazomethane for 30 min at 22°, then evaporated. The residue was chromatographed initially on alumina with ethyl acetate/hexane/methanol (80 : 20 : 5) as eluant, then on silica gel with ethyl acetate/hexane (3 : 7) as eluant. The product was isolated as an oil, 170 mg (41%).

(b) 2(S)-Hydroxy-3(R)-(3-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

A solution of the compound of example 3(a) (170 mg, 0.30 mmol) in 5 ml of ethanol was treated with 4 ml of 5% sodium hydroxide, and the mixture heated under argon at 65° for 1 hour. The solution was diluted with 10 ml of water, treated with activated charcoal, and filtered. The filtrate was acidified and extracted with chloroform. The extracts were washed with water, dried, and the solvent evaporated, giving the product as an oil, 137 mg (87%). nmr (CDCl₃) : 7.0-9.0 (m, overlapping broad s, 16H), 4.69 (d, 1H), 4.48 (d, 1H), 3.80 (d, 1H), 3.64 (d, 1H), 2.18-2.70 (m, 4H), 1.0-1.70 (m, 12H).

EXAMPLE 4**Preparation of 2-Hydroxy-3-(3-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid****(a) Methyl 2-Hydroxy-3-(3-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionate**

5 A solution of the compound in Example 1(c), (525 mg, 1.43 mmol) and m-mercaptobenzoic acid (331 mg, 2.15 mol) prepared according to Wiley, P.F., *J. Org. Chem.*, 16, 812 (1951) in a mixture of 4 ml of methanol and 0.5 ml of triethylamine was stirred at 23° for 16 hours. The reaction was poured into 0.5N HCl and extracted with ethyl acetate. The extracts were dried, evaporated, and the residue chromatographed over silica gel. The product, together with the regioisomeric compound, was eluted with ethyl acetate. The solvent was evaporated, and the residue dissolved in 10 ml of methanol, treated with 1 ml of 25% NaOMe in methanol, and stirred at 23° for 4 hours. The mixture was diluted with 0.5N HCl, and extracted with ethyl acetate. The extracts were dried, evaporated, and the residue chromatographed over silica gel. The product was eluted with a mixture of ethyl acetate, hexane, methanol, and acetic acid (75 : 25 : 5 : 1), and yielded after evaporation of the solvents 185 mg (25%).

(b) 2-Hydroxy-3-(3-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

20 A solution of the compound in example 4(a) (144 mg, 0.28 mmol) in 5 ml of ethanol was treated with 2 ml of 0.5N NaOH, and stirred at 23° for 2 hours. The reaction was diluted with 10 ml of water, filtered, the filtrate acidified, and extracted with ethyl acetate. The extracts were dried and evaporated and gave the titled product, 105 mg (75%) nmr (CDCl₃/Me₂CO) : 8.22(s, 1H), 6.70-8.10(m, 15H), 5.02(d, J = 4.3Hz, 1H), 4.64(d, J = 4.3Hz, 1H), 2.42-2.86(m, 4H), 1.16-1.74(m, 12H).

EXAMPLE 5**Preparation of 2-Hydroxy-3-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid****(a) Methyl 2-hydroxy-3-(4-carbomethoxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionate.**

30 A mixture of the compound of Example 1(c) (644 mg, 1.76 mmol) and p-mercaptobenzoic acid (325 mg, 2.11 mmol), prepared in a manner similar to the meta analog in Example 4(a), in 10 ml of methanol and 0.6 ml of triethylamine was stirred at 23° for 16 hours. The solution was treated with 1 ml of 25% NaOMe in methanol, stirred 3 hours, poured into 0.5 N hydrochloric acid and extracted with ethyl acetate. The extracts were dried and the solvent evaporated. The residue was esterified with methanol and gaseous HCl, and then chromatographed over silica gel. The product was eluted with a mixture of ethyl acetate and hexane (30 : 70), and gave 350 mg (37%). nmr CDCl₃ : 4.90(d, 1H), 4.50(t, 1H).

(b) 2-Hydroxy-3-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

40 The compound of Example 5(a) was hydrolyzed in the same manner as described for the preparation of the compound of example 4(b), in 48% yield after recrystallization from a mixture of benzene and hexane. nmr (CDCl₃/Me₂CO) : 8.00(d, 2H), 7.00-7.88(m, 14H), 5.12(d, J = 4.3Hz, 1H), 4.67(d, J = 4.3Hz, 1H), 2.40-2.90(m, 4H), 1.10-1.76 (m, 12H).

EXAMPLE 6**Preparation of 2-Hydroxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid**50 **acid****(a) Methyl 3-methoxy-4-mercaptomethylbenzoate**

55 A solution of 7.15 g (.027 mol) methyl 4-bromomethyl-3-methoxybenzoate in 50 ml of Me₂CO was treated with a solution of 2.1 g (.028 mol) thiourea in 50 ml Me₂CO and the reaction was stirred for 24 hours. The solid isothiuronium hydrobromide was filtered, washed with diethylether and dried. This salt was dissolved in 50 ml of water, treated with 50 ml 3N NaOH, and the mixture refluxed 3 hours under argon. The clear solution was cooled, acidified, and extracted with diethyl ether. The extracts were dried, and treated with an ethereal solution

of diazomethane for 30 minutes. Evaporation of the solvent gave methyl 3-methoxy-4-mercaptomethyl benzoate, 4.2 g (73%).

(b) Methyl 2-hydroxy-3-(4-carbomethoxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionate.

5 A solution of the compound in Example 1(c) (980 mg, 2.68 mmol) and methyl 4-mercaptomethyl-3-methoxy benzoate (625 mg, 2.95 mmol) in 10 ml of methanol and 2 ml of triethylamine were stirred for 16 hours at 23° and then evaporated. The residue was dissolved in diethyl ether, and washed with 0.5 N HCl. The diethylether layer was dried, and the solvent removed. The residue was dissolved in 15 ml of methanol, treated with 1 ml of 25% NaOMe in methanol, stirred at 23° for 2 hours, and poured into 0.5 N HCl. The mixture was extracted
10 with diethyl ether. The extracts were washed with water, dried and evaporated. The residue was chromatographed over silica gel. The products was eluted with a mixture of ethyl acetate and hexane (25 : 75), and gave 580 mg (38%). nmr (CDCl₃) : 4.70(t, J = 5.1Hz, 1H), 4.50(d, J = 5.1Hz, 1H).

15 (c) 2-Hydroxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

The compound of Example 6(b) was hydrolyzed in the same manner as described for the preparation of the compound in Example 4(b), in 28% yield after titration with a mixture of benzene and hexane. nmr(CDCl₃/D₂O) : 6.90-7.72(m, 12H), 4.70(d, J = 4.2Hz, 1H), 4.52(d, J = 4.2Hz, 1H), 3.34-3.95(m, 2H), 3.80(s,
20 3H), 2.20-2.68(m, 4H), 0.98-1.68(m, 12H).

In a similar manner the following was prepared : 2-hydroxy-3-(5-carboxy-2-methoxy-phenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid. nmr (CDCl₃) : 8.10(d, 1H), 7.90(d, 2H), 7.50(m, 1H), 6.88-7.22(m, 6H), 6.80(d, 2H), 4.76(d, 1H), 4.48(d, 1H), 3.81(s, 3H), 3.70 (d, 2H), 2.00-2.60 (m, 4H), 0.67-1.62(m, 12H).

25 EXAMPLE 7

Preparation of 2-Hydroxy-3-(4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

(a) Methyl-2-hydroxy-3-(4-carbomethoxyphenylmethyl thio)-3-[2-(8-phenyloctyl)phenyl]propionate.

30 A solution of the compound in Example 1(c), (880 mg, 2.40 mmol), and methyl p-mercaptomethylbenzoate (525 mg, 2.88 mmol), prepared similarly to the starting material of Example 6(a), in 10 ml of methanol and 0.4 ml of triethylamine was stirred at 23° for 2 days. 1 ml of 25% NaOMe in methanol was added, stirring was continued 45 minutes, and the reaction was poured into 0.5 N HCl and extracted with methylene chloride. The ext-
35 racts were dried and the solvents evaporated. The residue was chromatographed over a deactivated alumina column (25 ml H₂O/500 gm Al₂O₃). Impurities were removed with a mixture of ethyl acetate and hexane (1 : 4) and the product eluted with a mixture of methanol and ethyl acetate (1 : 19), and gave 620 mg (47%). nmr(CDCl₃) : 4.53(t, J = 4.5Hz, 1H), 4.40(d, J = 4.5Hz, 1H).

40 (b) 2-Hydroxy-3-(4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

The compound of Example 7(a) was hydrolyzed in the same manner as described for the preparation of the compound in Example 4 (b), in 46% yield after recrystallization from toluene. nmr (CDCl₃/Me₂CO) : 8.1-
45 9.9(broad, 3H), 8.02(d, J = 7.2Hz, 2H), 7.67(m, 1H), 7.42(d, J = 7.2Hz, 2H), 6.90-7.28(m, 8H), 4.72(d, J = 4.2Hz, 1H), 4.50(d, J = 4.2Hz, 1H), 3.92(d, J = 13Hz, 1H), 3.70(d, J = 13Hz, 1H), 2.26-2.70(m, 4H), 1.02-1.76(m, 12H).

EXAMPLE 8

50 Preparation of 2-Hydroxy-3-(2-fluoro-4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

(a) Methyl 2-Hydroxy-3-(2-fluoro-4-carbomethoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionate.

55 The compound of Example 1(c) was reacted with methyl 2-fluoro-4-mercaptomethylbenzoate, prepared in a manner similar to the starting material in Example 6(a), in an analogous manner to that described for the preparation of the compound described in Example 6(b), and gave the product in 22% yield. nmr(CDCl₃) : 4.63(t, J = 4.9Hz, 1H), 4.50(d, J = 4.9Hz, 1H).

(b) 2-Hydroxy-3-(2-fluoro-4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

The compound of Example 8(a) was hydrolyzed as described for the preparation of the compound described in Example 4(b). nmr(CDCI₃) : 6.98-7.90(m, 15H), 4.68(d, J = 4.6Hz, 1H), 4.55(d, J = 4.6Hz, 1H), 3.80(t, 2H), 2.25-2.70(m, 4H), 1.00-1.73(m, 12H).

EXAMPLE 9

Preparation of 2-Methoxy-3-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

(a) Methyl 2-methoxy-3-(4-carbomethoxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionate.

A solution of the compound in Example 5(a) (220 mg, 0.4 mmol) in 5 ml of tetrahydrofuran and 1 ml of dimethylformamide at 0° was treated with a 60% dispersion of sodium hydride in mineral oil (16 mg, 0.4 mmol). After 30 minutes, the solution was treated with iodomethane (58 mg, 0.4 mmol), stirring was continued at 23° for 1.5 hours, the reaction was poured into 0.5 N HCl and extracted with diethyl ether. The extracts were dried and evaporated. The residue was chromatographed initially over alumina and eluted with a mixture of ethyl acetate and hexane (35 : 65). The residue after evaporation of the solvents was chromatographed over a silica gel column. The product was eluted with a mixture of ethyl acetate and hexane 1 : 3, and gave 97 mg (44%). nmr (CDCl₃) : 4.90(d, J = 7.5Hz, 1H), 4.12(d, J = 7.5Hz, 1H), 3.82(s, 3H), 3.58(s, 3H), 3.24(s, 3H).

(b) 2-Methoxy-3-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

The compound of Example 9(a) was hydrolyzed in the same manner as described for the preparation of the compound in Example 4(b), in 64% yield after titration with a mixture of cyclohexane and hexane. nmr(CDCI₃) : 11.28(broad s, 2H), 7.82(d, 2H), 7.02-7.58(m, 11H), 5.10(d, J = 9.6Hz, 1H), 4.26(d, J = 9.6Hz, 1H), 3.20(s, 3H), 2.45-2.98(m, 4H), 1.18-1.90(m, 12H).

In a similar manner the following was prepared :

2-methoxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid ;
2-Methoxy-3-(4-carboxyphenylthio)-3[2-(3-phenylpropyl)phenyl]propionic acid ; and
2-Methoxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(14-phenyltetradecyl)phenyl]propionic acid.

EXAMPLE 10

Preparation of 2-Hydroxy-3-(4-hydroxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

(a) Methyl 2-hydroxy-3-(4-hydroxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionate

The compound of Example 1(c) (722 mg, 2 mmol) was dissolved in methanol (10 ml) containing 2% triethylamine and the solution was stirred under argon at room temperature. Triethylamine (1.68 ml, 12 mmol) and 4-hydroxythiophenol (428 mg, 3.4 mmol) were dissolved in methanol (15 ml) and added to the reaction mixture which was then stirred overnight at room temperature. The solvent was evaporated and the residue was flash chromatographed on 80 grams of silica gel eluted with 30% ethyl acetate/hexane to give a mixture of the desired product and its regioisomer, methyl 3-hydroxy-2-(4-hydroxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionate. The mixture of regioisomers was dissolved in methanol (20 ml) and stirred under argon at room temperature. Sodium methoxide, 25 wt. % in methanol, (0.92 ml, 4 mmol) was added dropwise and the mixture stirred for 2.5 hours. The mixture was cooled in an ice bath and acetic acid (0.3 ml, 5.2 mmol) was added dropwise. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to give the crude product which was flash chromatographed on 80 grams of silica gel eluted with 25% ethyl acetate/hexane to give the desired product.

(b) 2-Hydroxy-3-(4-hydroxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

The compound of example 10(a) (410 mg, 0.83 mmol) was dissolved in methanol (10 ml) and stirred under argon at ice bath temperature. A 1N solution of sodium hydroxide (4 ml, 4 mmol) was added and the mixture stirred overnight at room temperature. The solvent was evaporated and the residue was acidified with dilute hydrochloric acid. Extraction with ethyl acetate followed by drying the organic phase over anhydrous sodium

sulfate, filtration and evaporation gave the crude product which was recrystallized from ethyl acetate/hexane to give the desired product as a white crystalline solid, m.p. 155-157°C. Analysis for $C_{29}H_{34}O_4S$: Calculated: C, 72.77; H, 7.16; S, 6.70. Found: C, 72.90; H, 6.91; S, 6.95.

5 EXAMPLE 11

Preparation of 2-Methoxy-3-(4-carboxy-2-methoxyphenyl-methylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

10 (a) Methyl 2-methoxy-3-(4-carbomethoxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionate

The compound for Example 6(b) was reacted in the same manner as for the preparation of the compound of Example 9(a), and gave the product in 53% yield. nmr ($CDCl_3$): 4.48(d, J = 7.2Hz, 1H), 4.15(d, J = 7.2Hz, 1H), 3.90 (s, 3H), 3.85(s, 3H), 3.72(s, 3H), 3.33(s, 3H).

15 (b) 2-Methoxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

The compound of Example 11(a) was hydrolyzed as described for the preparation of the compound described in Example 4(b) to yield the desired product. nmr ($CDCl_3$): 4.52(d, J = 6.3Hz, 1H), 4.18(d, J = 6.3Hz, 1H), 3.86(s, 3H), 3.42(s, 3H).

20 EXAMPLE 12

Preparation of 3-(4-Carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid

25 A solution of 0.54 g (1.32 mmol) of tert-butyl 3-hydroxy-3-[2-(8-phenyloctyl)phenyl]propionate and 0.52 gm (2.64 mmol) of 3-methoxy-4-mercaptomethylbenzoic acid in 10 ml of methylene chloride at 0° was treated dropwise with 20 ml of trifluoroacetic acid. Stirring was continued at 0° for 4 hours and 22° for 1 hour, and all the solvents were thoroughly evaporated. The residue was crystallized first from $H_2O/MeCN$ (1:4), and then from Me_2CO /hexane, and to yield the product, 0.26 gm. nmr ($CDCl_3/Me_2CO/DMSO$): 7.05-7.72(m, 12H), 4.52 (d of d, 1H), 4.83(d, 1H), 4.82(s, 3H), 4.68(d, 1H), 2.88-3.24(m, 2H), 2.36-2.74 (m, 4H), 1.10-1.75(m, 12H).

30 EXAMPLE 13

Preparation of Methyl 2-hydroxy-3-mercapto-3-[2-(8-phenyloctyl)phenyl]propionate

35 (a) Methyl 2-hydroxy-3-(4-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionate

40 A solution of 4.54 gm (12.4 mmol) of the epoxyester of Example 1(c) and 1.91 gm (12.4 mmol) of p-methoxybenzyl mercaptan in a mixture of 1.7 ml of triethylamine and 20 ml of methanol were stirred for 42 hours, and the solvents evaporated. The residue was dissolved in diethyl ether and washed with 0.1N HCl. The organic layer was dried, and the solvent evaporated. The residue was chromatographed over an alumina column. Impurities and the undesired regioisomer were eluted with hexane/ethyl acetate/methanol (60:40:1). The desired product was eluted with hexane/ethyl acetate/methanol (40:60:2), 2.6 gm (40%). nmr ($CDCl_3$): 7.68(m, 1H), 7.20(m, 10H), 6.82(d, 2H), 4.58(t, 1H), 4.45 (d, 1H), 3.82 (s, 3H), 3.72 (s, 2H), 2.66(s, 3H), 3.14(d, 1H), 2.24-2.72 (m, 4H), 1.10-1.72 (m, 12H).

45 (b) Methyl 2-hydroxy-3-mercapto-3-[2-(8-phenyloctyl)phenyl]propionate

50 A solution of 1.1 gm (2.12 mmol) of the compound in Example 13(a) in 25 ml of methanol was treated with a solution of 2.02 gm (6.35 mmol) of mercuric acetate in 100 ml of methanol. After stirring 16 hours, the white precipitate was filtered and washed with diethyl ether. This mercuric salt was dissolved in 25 ml of hot dimethylformamide, 50 ml of methanol was added, and H_2S was bubbled into the solution for 30 minutes. The black precipitate was filtered, the filtrate was concentrated, diluted with water, and extracted with diethyl ether. The diethyl ether layer was washed well with water, dried, and the solvent evaporated. The residue was chromatographed over a silica gel column, and the product was eluted with a mixture of ethyl acetate/hexane (40:60, 370 mg (44%). nmr ($CDCl_3/D_2O$): 7.02-7.78 (m, 9H), 4.62 (s, 2H), 3.70 (s, 3H), 2.50-2.88 (m, 4H), 1.20-1.82 (m, 12H).

EXAMPLE 14**Preparation of 2-Hydroxy-3-(2-undecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid****(a) 2-Undecyloxybenzaldehyde**

To a stirred suspension of sodium hydride (10.0 mmol), which was prewashed with petroleum ether, in sieve dried dimethylformamide (10 ml) was added dropwise a solution of salicylaldehyde (10.1 mmol) in dimethylformamide (1 ml). To the reaction mixture was then added undecyl bromide (10.0 mmol) and the mixture stirred for 16 hours at ambient temperature under nitrogen. The reaction mixture was taken up in hexane (50 ml) and washed with 10 percent sodium hydroxide (2 x 50 ml) and saturated sodium chloride (50 ml). The organic phase was dried over anhydrous magnesium sulfate and charcoal. Evaporation of the volatiles yielded a colorless liquid which was purified by flash chromatography over silica gel with 2 percent ethyl acetate in hexane as eluant to afford the desired product as an oil.

Analysis for $C_{18}H_{28}O_2$: Calculated: C, 78.21; H, 10.21. Found: C, 77.92; H, 9.95.

(b) 2-Hydroxy-3-(2-undecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid

Employing the general methods of Example 1(c)-1(e), the compound of Example 14(a) is converted to the desired product.

The following compounds are prepared according to the general methods of Example 1(c)-1(e) from the appropriate alkyloxybenzaldehyde which is prepared by the general procedure of Example 14(a) from salicylaldehyde or 2-mercaptobenzaldehyde and the appropriate alkyl halide;

- 2-Hydroxy-3-(2-heptyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid;
- 2-Hydroxy-3-(2-dodecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid;
- 2-Hydroxy-3-(5-methoxy-2-dodecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid;
- 2-Hydroxy-3-(5-methyl-2-dodecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid;
- 2-Hydroxy-3-(5-fluoro-2-dodecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid;
- 2-Hydroxy-3-(5-chloro-2-dodecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid;
- 2-Hydroxy-3-(5-iodo-2-dodecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid;
- 2-Hydroxy-3-(5-bromo-2-dodecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid;
- 2-Hydroxy-3-(5-hydroxy-2-dodecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid;
- 2-Hydroxy-3-(5-nitro-2-dodecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid;
- 2-Hydroxy-3-(5-amino-2-dodecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid;
- 2-Hydroxy-3-(5-trifluoromethyl-2-dodecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid;
- 2-Hydroxy-3-(2-dodecyloxyphenyl)-3-(3-carboxyphenylthio)propionic acid is prepared from 2-(dodecylthio)benzaldehyde.
- 2-Hydroxy-3-(2-heptylthiophenyl)-3-(3-carboxyphenylthio)propionic acid is prepared from 2-(heptylthio)benzaldehyde.

EXAMPLE 15**Preparation of 2-Hydroxy-3-[2-6-phenylhexyloxy]phenyl]-3-(3-carboxyphenylthio)propionic acid****a) 2-(6-Phenylhexyloxy)benzaldehyde**

A solution of 6-phenylhexanoic acid (19.8 mmol) is sieve dried tetrahydrofuran (5 ml) was reduced with diborane in tetrahydrofuran (30 ml, 29.1 mmol) at 0°C for 4 hours to give 6-phenylhexanol. To an ice cold solution of the hexanol (ca. 19.8 mmol) and carbon tetrabromide (21.98 mmol) in methylene chloride (50 ml) was added triphenylphosphine (22.30 mmol) in methylene chloride (50 ml) and the resulting solution was stirred for 2.5 hours. The volatiles were evaporated and the residue was taken up in ether (100 ml), cooled in ice, and filtered. The filtrate was evaporated and distilled to afford 6-phenylhexyl bromide as an oil. A mixture of the bromide (8.00 mmol), salicylaldehyde (8.19 mmol) and potassium carbonate (9.33 mmol) in dimethylformamide (10 ml) was heated to 100°C and maintained at that temperature for one hour. The cooled reaction mixture was taken up in hexane (50 ml) and washed with 5% sodium hydroxide (50 ml) and saturated sodium chloride (50 ml). The organic phase was dried over anhydrous magnesium sulfate and charcoal. Evaporation yielded a colorless oil which was purified by flash chromatography over silica gel with 5% ethyl acetate in hexane as eluant to afford the desired product as an oil.

Analysis for $C_{19}H_{22}O_2$: Calculated : C, 80.82 ; H, 7.85. Found : C, 80.62 ; H, 7.72.

(b) 2-Hydroxy-3-[2-(6-phenylhexyloxy)phenyl]-3-(3-carboxyphenylthio)propionic acid

Employing the general methods of Example 1(c) through 1(e) the compound of Example 15(a) is converted to the desired product.

The following compounds are prepared according to the general methods described above from the appropriately substituted phenylalkoxybenzaldehyde.

2-Hydroxy-3-[2-(3-phenylpropyloxy)phenyl]-3-(3-carboxyphenylthio)propionic acid ; and
2-Hydroxy-3-[2-(9-phenylnonyloxy)phenyl]-3-(3-carboxyphenylthio)propionic acid.

EXAMPLE 16

Preparation of 3-[2-(6-phenylthiohexylthio)phenyl]-3-(2-carboxyphenylthio)-2-hydroxypropionic acid

a) Preparation of 2-(6-thiophenoxyhexylthio)-benzoic acid

Thiosalicylic acid (1.3 g, 0.008 mole) and 6-thio-phenoxyhexylbromide (2.5 g, 0.009 mole) are dissolved in dimethylformamide (50 ml) and the solution is stirred under argon. Potassium carbonate (1.5 g, 0.011 mole) is added carefully to the reaction. After the addition is complete the mixture is slowly warmed to 100°C. The solvents are evaporated, and the residue is dissolved in water, acidified with dilute hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue is flash chromatographed on silica gel to give the desired product.

b) Preparation of 2-(6-phenylthiohexylthio)benzyl alcohol.

To a suspension of lithium aluminum hydride (0.292 g, 0.007 mole) in tetrahydrofuran (30 ml) is added a solution of 2-(6-thiophenoxyhexylthio)benzoic acid (2.42 g, 0.007 mole) in tetrahydrofuran (30 ml). The reaction is stirred at room temperature under argon, overnight. When the reaction is complete several drops of ice water are added followed by cold 10% sodium hydroxide (approximately 1.0 ml), followed by cold 10% sodium hydroxide (approximately 1.0 ml), followed by more ice water. This produces a dry granular precipitate which is filtered and is washed. The filtrate is then dried over magnesium sulfate, filtered and is evaporated. The crude alcohol is flash chromatographed on silica gel to give the desired compound.

c) Preparation 2-(6-phenylthiohexylthio)-benzaldehyde

To a suspension of manganese dioxide (11.78 g, 0.135 mole) in ethyl acetate (30 ml) is added a solution of 2-(6-thiophenoxyhexylthio)benzyl alcohol (1.23 g ; 0.0037 mole) in ethyl acetate (20 ml). The reaction is stirred at room temperature under argon for 1.5 hours. The suspension is then filtered. The filtrate is dried over magnesium sulfate, filtered and evaporated providing the desired compound.

d) Methyl trans-3-[2-(6-phenylthiohexylthio)phenyl]-2,3-epoxypropionate

The compound of Example 16(c) (10 mmol) is dissolved in diethyl ether (25 ml) and the solution is stirred under argon at 0°C. Methyl chloroacetate (15 mmol) is added followed by the addition of sodium methoxide (15 mmol). The mixture is stirred for 2.5 hours at ice bath temperature. A small quantity of water is added, the ether phase is separated, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue is flash chromatographed on 80 grams of silica gel eluted with 5-30% ethyl acetate/hexane to give the product.

(e) Methyl 3-[2-(6-phenylthiohexylthio)phenyl]-3-(2-carboxyphenylthio)-2-hydroxypropionate

A solution of the compound of Example 16(d) (1.39 mmol), 2-mercaptobenzoic acid (1.53 mmol) and triethylamine (3.06 mmol) in 10 ml of methanol are stirred overnight at 22° under argon. The mixture is poured into water, acidified with 1N hydrochloric acid, and is extracted with diethylether. The extracts are dried and the solvent evaporated. The residue is chromatographed on silica gel to remove starting materials and the product is eluted with a mixture of ethyl acetate, hexane, and methanol (60 : 40 : 2.5). The solvents are evaporated, and the residue is recrystallized from methanol to yield the product.

f) 3-[2-(6-phenylthiohexylthio)phenyl]-3-(2-carboxyphenylthio)-2-hydroxypropionic acid

A suspension of the compound of Example 16(e) (0.44 mmol), 5 ml of methanol, 2 ml of water and 2.5N sodium hydroxide is heated at 95° for 10 minutes, and is stirred at 22° for 2 hours. The mixture is diluted with 20 ml of water and filtered. The filtrate is acidified, and extracted with ethyl acetate. The extracts are washed with water, dried, and the solvent evaporated. The residue is recrystallized from acetonitrile to give the desired product.

EXAMPLE 17

10 Preparation of 2-Hydroxy-3-(2-carboxy-4-oxo-8-propyl-4H-1-benzopyran-7-ylthio)-3-[2-(8-phenyloctyl)phenyl] propionic acid

(a) Ethyl 7-((dimethylamino)thioxomethoxy)-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylate

15 Ethyl 7-hydroxy-4-oxo-8-n-propyl-4H-1-benzopyran-2-carboxylate (1 g) in anhydrous dimethylformamide (4 ml) is cooled to 0° and treated under nitrogen with sodium hydride (50% dispersion in mineral oil, 180 mg) with stirring for 30 minutes. Dimethylaminothiocarbonylchloride (465 mg) is added and the mixture is stirred 15 minutes at 0°, warmed to 80° and maintained as such for 18 hours. The mixture is cooled, diluted with 20 methylene chloride (50 ml) and washed with water (3 x 100 ml), dried over sodium sulfate and reduced to dryness in vacuo. The residue is recrystallized from ethyl acetate and hexane to yield the title compound.

(b) Ethyl 7-(((dimethylamino)carbonyl)thio)-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylate

25 The ester prepared in Example 17(a) is heated neat under a nitrogen atmosphere at 200° for 2 hours. After cooling the residue is crystallized from ethyl acetate and hexane to yield the title compound.

(c) 7-Mercapto-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylic acid

30 Sodium (690 mg) is dissolved in anhydrous methanol (50 ml) and to this is added the compound of Example 17(b). The mixture is stirred under a nitrogen atmosphere for 3 hours at ambient temperature. Water (50 ml) is added and the mixture is acidified with 6N HCl. The resulting crystals are collected by filtration and recrystallized from ethyl acetate to provide the title compound.

35 (d) Methyl 2-hydroxy-3-(2-carboxy-4-oxo-8-propyl-4H-1-benzopyran-7-yl thio)-3-[2-(8-phenyloctyl) phenyl] propionate

40 The compound of Example 1(c), methyl trans-3-[2-(8-phenyloctyl)phenyl]-2,3-epoxypropionate, is reacted with the 7-mercapto-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylic acid of Example 17(c) in an analogous manner to that for the preparation of the compound in Example 1(d) to yield the desired product.

(e) 2-Hydroxy-3-(2-carboxy-4-oxo-8-propyl-4H-1-benzopyran-7-yl thio)-3-[2-(8-phenyloctyl)phenyl] propionic acid.

45 The compound from Example 18(d) is hydrolyzed with aqueous NaOH in an analogous manner to that for the preparation of the compound in Example 1(e) to yield to desired product.

EXAMPLE 18

50 As a specific embodiment of a composition of this invention, 1 to 10 mg/ml of an active ingredient, such as the compound of Example 1 is dissolved in isotonic saline solution and aerosolized from a nebulizer operating at an air flow adjusted to deliver the desired aerosolized weight of drug.

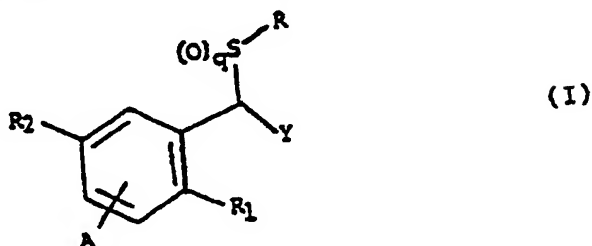
EXAMPLE 19

55 As an additional embodiment of a composition of this invention 100 mg of an active ingredient, such as the compound of Example 4, 13 or 14 is combined with 4 mg of chlorpheniramine maleate with a suitable carrier or excipient.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound represented by the following structural formula (I) :



wherein

q is 0, 1, or 2 ;

R₁ is (L)_a-(CH₂)_b-(T)_c-M

a is 0 or 1 ;

b is 3 to 14 ;

c is 0 or 1 ;

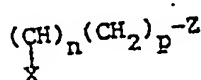
L and T are independently sulfur, oxygen, or CH₂ with the proviso that L and T are not sulfur when q is 1 or 2 ; and

M is C₁₋₄ alkyl, ethynyl, trifluoromethyl, isopropenyl, furanyl, thienyl, cyclohexyl or phenyl optionally mono-substituted with Br, Cl, CF₃, C₁₋₄ alkoxy, C₁₋₄ alkyl, methylthio, or trifluoromethylthio ;

R₂ and A are independently selected from H, CF₃, C₁₋₄alkyl, C₁₋₄alkoxy, F, Cl, Br, I, OH, NO₂ or NH₂ ; or R₁ and A are H and

R₂ is (L)_a-(CH₂)_b-(T)_c-M wherein a, b, c, L, T, and M are as defined above ;

Y is COR₃ or



wherein

R₃ is OH, NH₂, aryloxy, or C₁₋₆ alkoxy ;

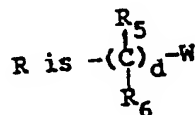
n is 0 or 1 ;

p is 0, or 1 or 2 ;

X is H, OH, C₁₋₄ alkyl, C₁₋₄ alkoxy,

or F ; and

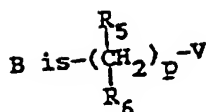
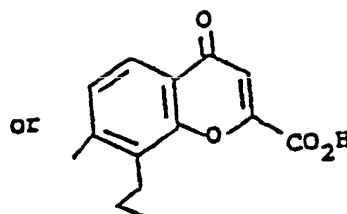
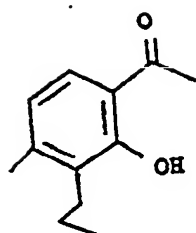
Z is COR₃, or tetrazolyl ;



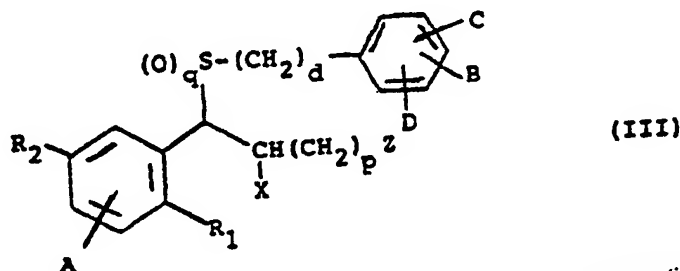
R₅ and R₆ are independently hydrogen or C₁₋₄ alkyl at any point when d is not 0 ;

d is 0 to 6 ;

W is a six membered aryl or heteroaryl ring selected from phenyl, pyridyl, or pyrimidyl, unsubstituted or substituted with B, C, or D ; or W is one of



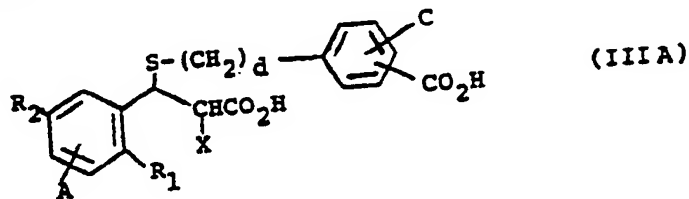
wherein
 R_5 and R_6 are independently hydrogen or C_{1-4} alkyl; p is 0 to 6; V is H, C_{1-4} alkyl, COR_3 , SO_3H , SO_2H ,
 SO_2NH_2 , $COCH_2OH$, $CHOHCH_2OH$, or tetrazolyl, with R_3 as defined above;
 C and D are independently selected from H, OH, F, Cl, Br, CF_3 , C_{1-4} alkyl, C_{1-4} alkoxy, methylthio, trifluoromethylthio, NO_2 , NH_2 , NHC_{1-4} alkyl, or C_{1-4} alkylCO—;
 or a pharmaceutically acceptable salt thereof.
 2. A compound of Claim 1 represented by the following structural formula (III):



wherein R_1 , R_2 , A, B, C, D, X, Z, p, q, and d are as defined in Claim 1, or a pharmaceutically acceptable salt thereof.

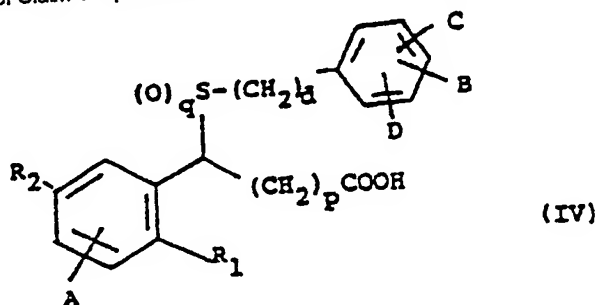
3. A compound of Claim 2 which is 2-hydroxy-3-(4-hydroxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

4. A compound of Claim 2 represented by the following structural formula (IIIA)

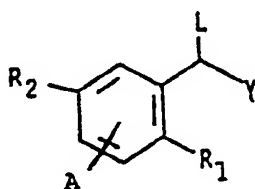


wherein
 X is OH, H, or OCH_3 ;
 d is 0 or 1; and
 R_1 , R_2 , A, and C are as defined in claim 2; or a pharmaceutically acceptable salt thereof.
 5. A compound of Claim 4 which is:
 2-hydroxy-3-(2-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 2(S)-hydroxy-3(R)-(2-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 2(S)-hydroxy-3(R)-(3-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;
 2-hydroxy-3-(3-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid;

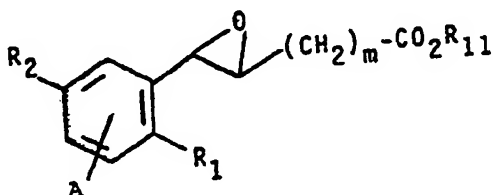
- 2-hydroxy-3-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid ;
 2-hydroxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid ;
 2-hydroxy-3-(4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid ;
 2-hydroxy-3-(2-fluoro-4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid ;
 2-methoxy-3-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid ;
 2-methoxy-3-[4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid ;
 2-hydroxy-3-(5-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.
 6. A compound of Claim 1 represented by the following structural formula (IV) :



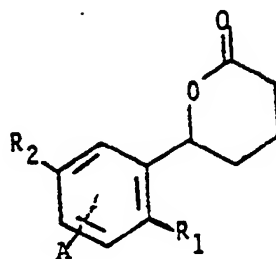
- wherein R_1 , R_2 , A, B, C, D, q, and d, are as defined in Claim 1 and p is 1 or 2.
 7. A compound of Claim 6 which is 3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.
 8. A pharmaceutical composition comprising a pharmaceutical carrier or diluent and a nontoxic effective amount of a compound of Claim 1.
 9. The composition of Claim 8 in a form suitable for administration orally, parenterally, topically, or by inhalation in which the active component is
 2-hydroxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid, or
 2-hydroxy-3-(2-fluoro-4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.
 10. A pharmaceutical composition for inhibiting antigen-induced respiratory anaphylaxis comprising a pharmaceutical carrier or diluent and nontoxic amounts sufficient to produce said inhibition of a compound of Claim 1, and an histamine H_1 -receptor antagonist.
 11. A compound according to any one of Claims 1 to 7 for use in therapy.
 12. A process for the preparation of a compound of claim 1, formula (I) which comprises reacting an appropriately protected substituted thiol, RSH , wherein R is as defined in Claim 1, with :
 (a) a compound of the formula :



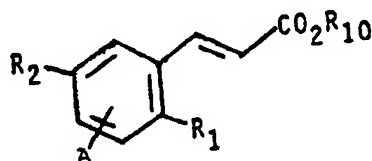
- wherein R_1 and R_2 are as defined in Claim 1, L is a leaving group selected from chloro, bromo or hydroxy;
 Y is CO_2R_{10} or $CH(R_{12})CO_2R_{10}$ wherein R_{10} is an ester protective group and R_{12} is hydrogen, methyl, methoxy or fluoro, to form compounds wherein Y is CO_2H or $CH(R_{12})CO_2H$;
 (b) a compound for the formula :



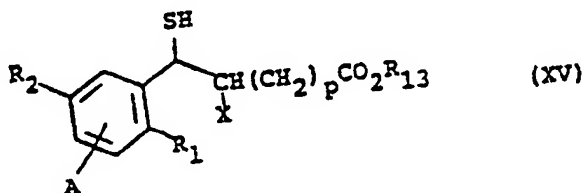
wherein R_1 , R_2 and m are as defined in Claim 1, and R_{11} is lower alkyl, to form compounds wherein Y is $CH(OH)(CH_2)_mCO_2H$;
 (c) a compound of the formula :



wherein R_1 and R_2 are as defined in claim 1 to form compounds wherein Y is $(CH_2)_3CO_2H$; and
 (d) a compound of the formula :



wherein R_1 and R_2 are as defined in claim 1 and R_{10} is an ester protective group, to form compounds wherein Y is CH_2CO_2H ;
 followed by removal of any protective groups, optionally resolving any diastereomeric mixture of compounds and optionally forming a pharmaceutically acceptable salt.
 13. A compound represented by the following structural formula (XV) :



wherein

R_1 is $(L)_a(CH_2)_b(T)_cM$

a is 0 or 1

b is 3 to 14 ;

c is 0 or 1 ;

L and T are independently sulfur, oxygen, or CH_2 ;

M is C_{1-4} alkyl, ethynyl, trifluoromethyl, isopropenyl, furanyl, thienyl, cyclohexyl or phenyl optionally mono-substituted with Br, Cl, CF_3 , C_{1-4} alkoxy, C_{1-4} alkyl, methylthio, or trifluoromethylthio ;

R_2 and A are independently selected from H, CF_3 , C_{1-4} alkyl, C_{1-4} alkoxy, F, Cl, Br, I, OH, NO_2 or NH_2 ;

or R_1 and A are H and

R_2 is $(L)_a(CH_2)_b(T)_cM$ wherein a , b , c , L , T , and M are as defined above ;

R_{13} is C_{1-8} alkyl ;

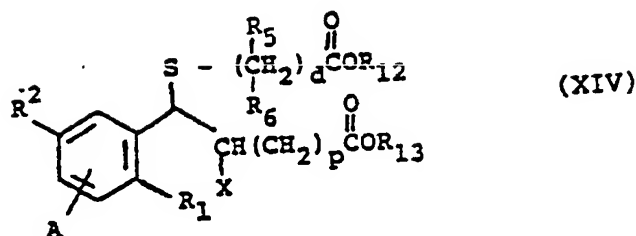
p is 0, 1, or 2 ; and

X is OH.

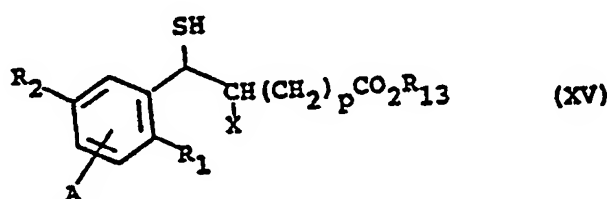
14. The compound of claim 13 which is methyl 2-hydroxy-3-mercapto-3-[2-(8-phenyloctyl)phenyl]propionate.

15. A process for preparation of a compound of Claim 1 comprising :

a) reacting a strong base with a compound having the following structural formula (XIV)



wherein d is 2; X is OH; one of R₅ or R₆ adjacent to the ester group is H and the other is H or C₁₋₄ alkyl; R₁, R₂, A, and p are as defined in Claim 1 and R₁₂ and R₁₃ are independently selected from C₁₋₄ alkyl to yield a thiol represented by the following structural formula (XV)



wherein R₁, R₂, R₁₃, A, X, and p are defined as above for formula (XIV);

b) reacting the thiol of formula (XV) with an alkylating agent or Michael acceptor to yield a compound of Formula (I).

16. The process of Claim 15 wherein the alkylating agent is an alkyl halide and the strong base is sodium hydride.

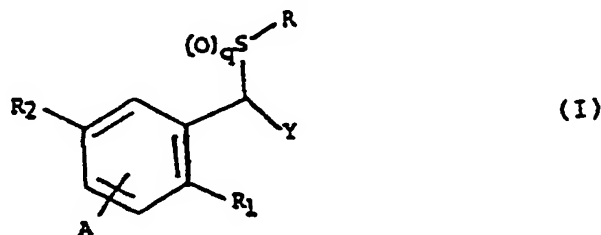
17. The process of Claim 15 wherein the Michael acceptor is an α , β -unsaturated carbonyl compound, or an alkyne containing a conjugated carbonyl group.

18. A compound of claim 2 which is methyl 2-hydroxy-3-(4-carbomethoxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionate; methyl 2-hydroxy-3-(2-fluoro-4-carbomethoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionate; or methyl 2-methoxy-3-(4-carbomethoxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionate.

19. A compound according to any one Claims 1 to 7 for use in the treatment of diseases in which leukotrienes are a factor.

Claims for the following Contracting State : ES

1. A process for the preparation of compounds represented by the following structural formula (I) :



wherein

q is 0, 1, or 2;

R₁ is (L)_a-(CH₂)_b-(T)_c-M

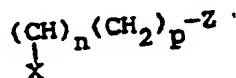
a is 0 or 1;

b is 3 to 14;

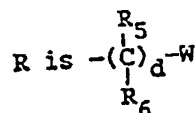
c is 0 or 1;

L and T are independently sulfur, oxygen, or CH₂ with the proviso that L and T are not sulfur when q is 1

or 2 ;
 M is C₁₋₄ alkyl, ethynyl, trifluoromethyl, isopropenyl, furanyl, thienyl, cyclohexyl or phenyl optionally mono-
 substituted with Br, Cl, CF₃, C₁₋₄ alkoxy, C₁₋₄ alkyl, methylthio, or trifluoromethylthio ;
 R₂ and A are independently selected from H, CF₃, C₁₋₄ alkyl, C₁₋₄ alkoxy, F, Cl, Br, I, OH, NO₂ or NH₂ ;
 or R₁ and A are H and
 R₂ is (L)_a-(CH₂)_b-(T)_c-M wherein a, b, c, L, T, and M are defined above ;
 Y is COR₃ or

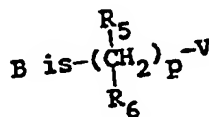
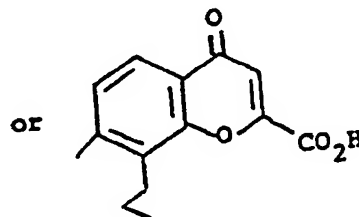
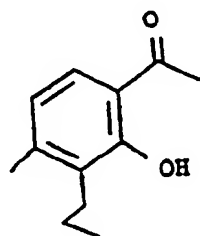


wherein
 R₃ is OH, NH₂, aryloxy, or C₁₋₆ alkoxy ;
 n is 0 or 1 ;
 p is 0, 1 or 2 ;
 X is H, OH, C₁₋₄ alkyl, C₁₋₄ alkoxy, or F ; and
 Z is COR₃, or tetrazolyl ;

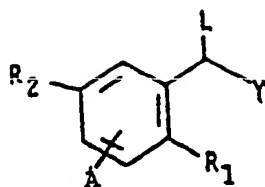


R₅ and R₆ are independently hydrogen or C₁₋₄ alkyl at any point when d is not 0 ;
 d is 0 to 6 ;

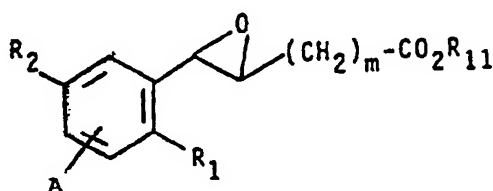
W is a six membered aryl or heteroaryl ring selected from phenyl, pyridyl, or pyrimidyl, unsubstituted or
 substituted with B, C, or D ; or W is one of



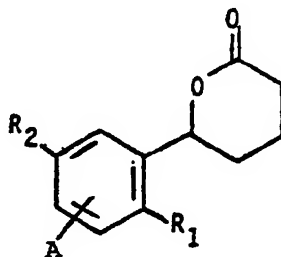
wherein
 R₅ and R₆ are independently hydrogen or C₁₋₄ alkyl ; p is 0 to 6 ; V is H, C₁₋₄ alkyl, COR₃, SO₃H, SO₂H,
 SO₂NH₂, COCH₂OH, CHOHCH₂OH, or tetrazolyl, with R₃ as defined above ;
 C and D are independently selected from H, OH, F, Cl, Br, CF₃, C₁₋₄ alkyl, C₁₋₄ alkoxy, methylthio, trifluoromethylthio, NO₂, NH₂, NHC₁₋₄ alkyl, or C₁₋₄ alkylCO— ;
 or a pharmaceutically acceptable salt thereof, which comprises reacting an appropriately protected substituted thiol, RSH, wherein R is as defined above with :
 (a) a compound of the formula :



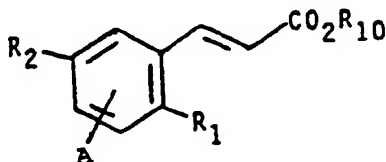
wherein R_1 and R_2 are as defined in Claim 1, L is a leaving group selected from chloro, bromo or hydroxy;
 Y is CO_2R_{10} or $\text{CH}(\text{R}_{12})\text{CO}_2\text{R}_{10}$
 wherein R_{10} is an ester protective group and R_{12} is hydrogen, methyl or fluoro, to form compounds wherein
 Y is CO_2H or $\text{CH}(\text{R}_{12})\text{CO}_2\text{H}$;
 (b) a compound of the formula :



wherein R_1 , R_2 and m are as defined above, and R_{11} is lower alkyl, to form compounds wherein Y is
 $\text{CH}(\text{OH})(\text{CH}_2)_m\text{CO}_2\text{H}$;
 (c) a compound of the formula :



wherein R_1 and R_2 are as defined above, to form compounds wherein Y is $(\text{CH}_2)_3\text{CO}_2\text{H}$; and
 (d) a compound of the formula :



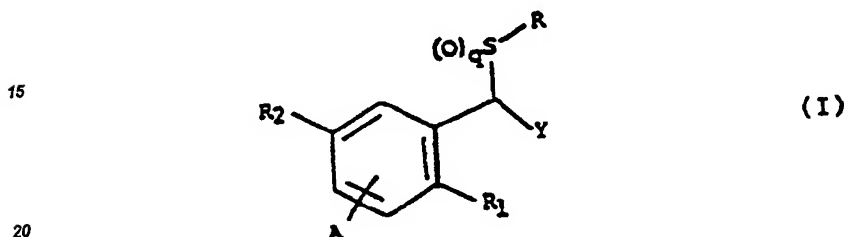
wherein R_1 and R_2 are as defined above and R_{10} is an ester protective group, to form compounds wherein
 Y is $\text{CH}_2\text{CO}_2\text{H}$;

followed by removal of any protective groups, optionally resolving any diastereomeric mixture of com-
 pounds and optionally forming a pharmaceutically acceptable salt.

2. The process of Claim 1(b) wherein methyl trans-3-[2-(8-phenyloctyl)phenyl]-2,3-epoxypropionate and
 methyl 4-mercaptomethyl-3-methoxybenzoate are reacted to give 2-hydroxy-3-(4-carboxy-2-
 methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

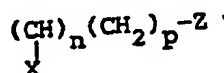
3. The process of Claim 1(b) wherein methyl trans-3-[2-(8-phenyloctyl)phenyl]-2,3-epoxypropionate and
 p-mercaptobenzoic acid are reacted to give methyl 2-hydroxy-3-(4-carbomethoxyphenylthio)-3-[2-(8-phenyloctyl)
 phenyl]propionate, which is then reacted with sodium hydride and iodomethane to yield 2-methoxy-3-(4-
 carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

4. The process of claim 1(b) wherein methyl trans-3-[2-(8-phenyloctyl)phenyl]-2,3-epoxypropionate and methyl 2-fluoro-4-mercaptomethylbenzoate are reacted to give 2-hydroxy-3-(2-fluoro-4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.
5. The process of claim 3 wherein the erythro mixture of diastereomers is resolved to give 2(S)-methoxy-3(R)-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.
6. The processes of claims 2, 3 or 4 wherein the product is converted to its disodium salt.
7. A process for the preparation of a pharmaceutical composition which comprises admixing a pharmaceutical carrier or diluent and a compound as defined in claim 1, formula (I).
8. A process for the preparation of a pharmaceutical composition which comprises admixing a pharmaceutical carrier or diluent, a compound as defined in claim 1, formula (I), and an histamine H₁-receptor antagonist.
9. A process for the preparation of a compound represented by the following structural formula (I) :



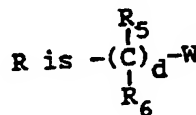
wherein

- q is 0, 1, or 2 ;
- R₁ is (L)_a-(CH₂)_b-(T)_c-M
- a is 0 or 1 ;
- b is 3 to 14 ;
- c is 0 or 1 ;
- L and T are independently sulfur, oxygen, or CH₂ with the proviso that L and T are not sulfur when q is 1 or 2 ;
- M is C₁₋₄ alkyl, ethynyl, trifluoromethyl, isopropenyl, furanyl, thienyl, cyclohexyl or phenyl optionally mono-substituted with Br, Cl, CF₃, C₁₋₄ alkoxy, C₁₋₄ alkyl, methylthio, or trifluoromethylthio ;
- R₂ and A are independently selected from H, CF₃, C₁₋₄ alkyl, C₁₋₄ alkoxy, F, Cl, Br, I, OH, NO₂ or NH₂ ;
- or R₁ and A are H and
- R₂ is (L)_a-(CH₂)_b-(T)_c-M wherein a, b, c, L, T, and M are as defined above ;
- Y is COR₃ or



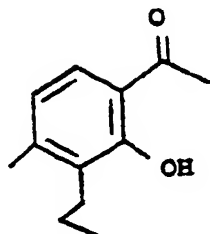
wherein

- R₃ is OH, NH₂, aryloxy, or C₁₋₈ alkoxy ;
- n is 0 or 1 ;
- p is 0, 1 or 2 ;
- X is H, OH, C₁₋₄ alkyl, C₁₋₄ alkoxy, or F ; and
- Z is COR₃, or tetrazolyl ;

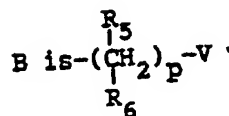
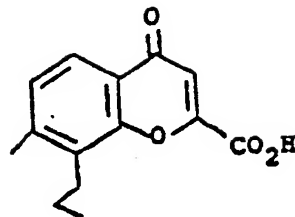


- R₅ and R₆ are independently hydrogen or C₁₋₄ alkyl at any point when d is not 0 ;
- d is 0 to 6 ;
- W is a six membered aryl or heteroaryl ring selected from phenyl, pyridyl, or pyrimidyl, unsubstituted or

substituted with B, C, or D ; or W is one of

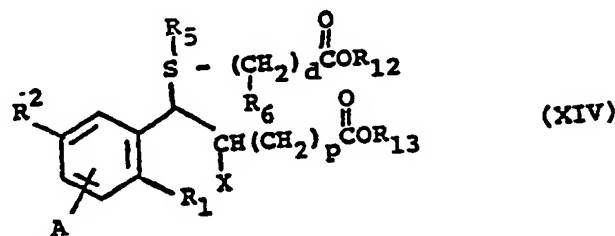


or

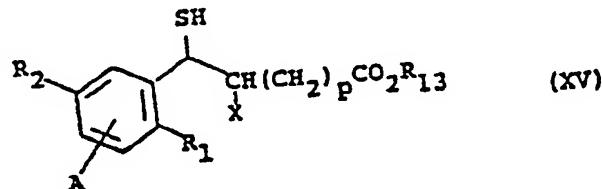


wherein

R_5 and R_6 are independently hydrogen or C_{1-4} alkyl ; p is 0 to 6 ; V is H, C_{1-4} alkyl, COR_3 , SO_3H , SO_2H , SO_2NH_2 , $COCH_2OH$, $CHOHCH_2OH$, or tetrazolyl, with R_3 as defined above ;
 C and D are independently selected from H, OH, F, Cl, Br, CF_3 , C_{1-4} alkyl, C_{1-4} alkoxy, methylthio, trifluoromethylthio, NO_2 , NH_2 , NHC_{1-4} alkyl, or C_{1-4} alkylCO— ;
 or a pharmaceutically acceptable salt thereof, comprising
 a) reacting a strong base with a compound having the following structural formula (XIV)



wherein d is 2 ; X is OH ; one of R_5 or R_6 adjacent to the ester group is H and the other is H or C_{1-4} alkyl ;
 R_1 , R_2 , A , and p are as defined above and R_{12} and R_{13} are independently selected from C_{1-4} alkyl to yield
 a thiol represented by the following structural formula (XV)



wherein R_1 , R_2 , R_{13} , A , X , and p are defined as above for formula (XIV) ;

b) reacting the thiol of formula (XV) with an alkylating agent or Michael acceptor to yield a compound of Formula (I).

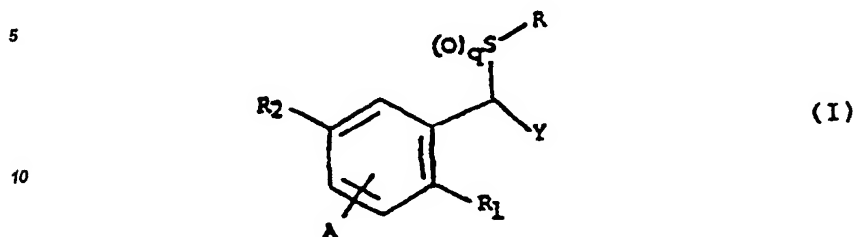
10. The process of Claim 9 wherein the alkylating agent is an alkyl halide.

11. The process of Claim 9 wherein the strong base is sodium hydride.

12. The process of Claim 9 wherein the Michael acceptor is an α , β -unsaturated carbonyl compound, or an alkyne containing a conjugated carbonyl group.

Claims for the following Contracting State : GR

1. A process for the preparation of compounds represented by the following structural formula (I) :



15 wherein

q is 0, 1, or 2 ;

R₁ is (L)_a-(CH₂)_b-(T)_c-M

a is 0 or 1 ;

b is 3 to 14 ;

c is 0 or 1 ;

20 L and T are independently sulfur, oxygen, or CH₂ with the proviso that L and T are not sulfur when q is 1 or 2 ;

M is C₁₋₄ alkyl, ethynyl, trifluoromethyl, isopropenyl, furanyl, thienyl, cyclohexyl or phenyl optionally mono-substituted with Br, Cl, CF₃, C₁₋₄ alkoxy, C₁₋₄ alkyl, methylthio, or trifluoromethylthio ;

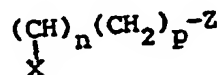
25 R₂ and A are independently selected from H, CF₃, C₁₋₄ alkyl, C₁₋₄ alkoxy, F, Cl, Br, I, OH, NO₂ or NH₂ ;

or R₁ and A are H and

R₂ is (L)_a-(CH₂)_b-(T)_c-M wherein a, b, c, L, T, and M are as defined above ;

Y is COR₃ or

30



35

wherein

R₃ is OH, NH₂, aryloxy, or C₁₋₆ alkoxy ;

n is 0 or 1 ;

p is 0, 1 or 2 ;

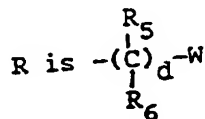
X is H, OH, C₁₋₄ alkyl, C₁₋₄ alkoxy,

40

or F ; and

Z is COR₃, or tetrazolyl ;

45



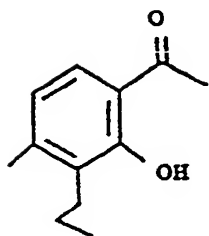
R₅ and R₆ are independently hydrogen or C₁₋₄ alkyl at any point when d is not 0 ;

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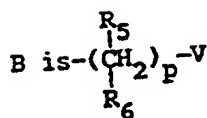
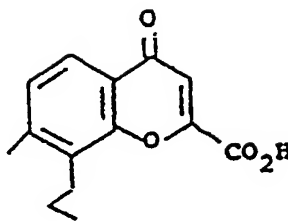
d is 0 to 6 ;

W is a six membered aryl or heteroaryl ring selected from phenyl, pyridyl, or pyrimidyl, unsubstituted or substituted with B, C, or D ; or W is one of

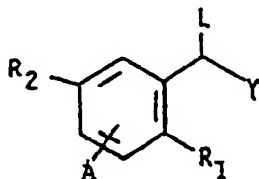
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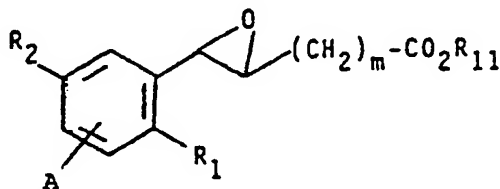
or



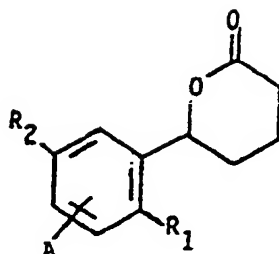
wherein
 R_5 and R_6 are independently hydrogen or C_{1-4} alkyl; p is 0 to 6; V is H, C_{1-4} alkyl, COR_3 , SO_3H , SO_2H ,
 SO_2NH_2 , $COCH_2OH$, $CHOHCH_2OH$, or tetrazolyl, with R_3 as defined above;
 C and D are independently selected from H, OH, F, Cl, Br, CF_3 , C_{1-4} alkyl, C_{1-4} alkoxy, methylthio, trifluoromethylthio, NO_2 , NH_2 , NHC_{1-4} alkyl, or C_{1-4} alkylCO—;
 or a pharmaceutically acceptable salt thereof, which comprises reacting an appropriately protected substituted thiol, RSH , wherein R is as defined above with:
 (a) a compound of the formula:



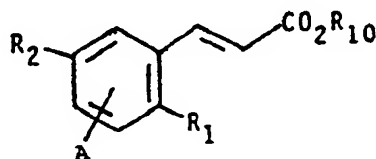
wherein R_1 and R_2 are as defined in Claim 1, L is a leaving group selected from chloro, bromo or hydroxy;
 Y is CO_2R_{10} or $CH(R_{12})CO_2R_{10}$
 wherein R_{10} is an ester protective group and R_{12} is hydrogen, methyl or fluoro, to form compounds wherein
 Y is CO_2H or $CH(R_{12})CO_2H$;
 (b) a compound of the formula:



wherein R_1 , R_2 and m are as defined above, and R_{11} is lower alkyl, to form compounds wherein Y is
 $CH(OH)(CH_2)_mCO_2H$;
 (c) a compound of the formula:



wherein R_1 and R_2 are as defined above, to form compounds wherein Y is $(CH_2)_3CO_2H$; and
(d) a compound of the formula :



wherein R_1 and R_2 are as defined above and R_{10} is an ester protective group, to form compounds wherein Y is CH_2CO_2H ;

followed by removal of any protective groups, optionally resolving any diastereomeric mixture of compounds and optionally forming a pharmaceutically acceptable salt.

2. The process of Claim 1(b) wherein methyl trans-3-[2-(8-phenyloctyl)phenyl]-2,3-epoxypropionate and methyl 4-mercaptomethyl-3-methoxybenzoate are reacted to give 2-hydroxy-3-(4-carboxy-2-methoxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

3. The process of Claim 1(b) wherein methyl trans-3-[2-(8-phenyloctyl)phenyl]-2,3-epoxypropionate and p-mercaptobenzoic acid are reacted to give methyl 2-hydroxy-3-(4-carbomethoxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionate, which is then reacted with sodium hydride and iodomethane to yield 2-methoxy-3-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

4. The process of claim 1(b) wherein methyl trans-3-[2-(8-phenyloctyl)phenyl]-2,3-epoxypropionate and methyl 2-fluoro-4-mercaptomethylbenzoate are reacted to give 2-hydroxy-3-(2-fluoro-4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

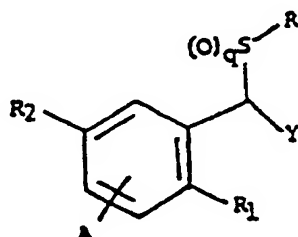
5. The process of claim 3 wherein the erythro mixture of diastereomers is resolved to give 2(S)-methoxy-3(R)-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionic acid.

6. The processes of claims 2, 3 or 4 wherein the product is converted to its disodium salt.

7. A process for the preparation of a pharmaceutical composition which comprises admixing a pharmaceutical carrier or diluent and a compound as defined in claim 1, formula (I).

8. A process for the preparation of a pharmaceutical composition which comprises admixing a pharmaceutical carrier or diluent, a compound as defined in claim 1, formula (I) and an histamine H_1 -receptor antagonist.

9. A process for the preparation of a compound represented by the following structural formula (I) :



(I)

wherein

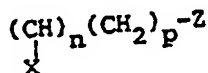
q is 0, 1, or 2 ;

R_1 is $(L)_a-(CH_2)_b-(T)_c-M$

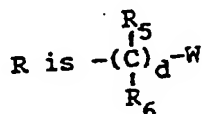
a is 0 or 1 ;

b is 3 to 14 ;

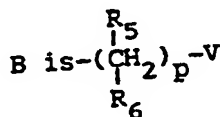
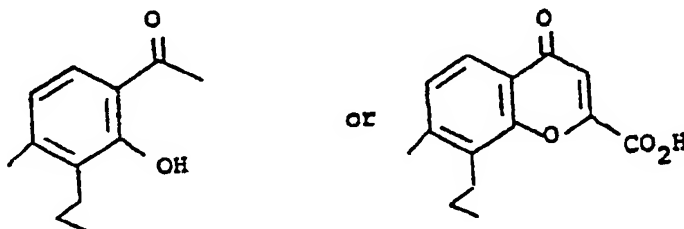
c is 0 or 1 ;
 L and T are independently sulfur, oxygen, or CH₂ with the proviso that L and T are not sulfur when q is 1
 or 2 ;
 M is C₁₋₄ alkyl, ethynyl, trifluoromethyl, isopropenyl, furanyl, thienyl, cyclohexyl or phenyl optionally mono-
 substituted with Br, Cl, CF₃, C₁₋₄ alkoxy, C₁₋₄ alkyl, methylthio, or trifluoromethylthio ;
 R₂ and A are independently selected from H, CF₃, C₁₋₄ alkyl, C₁₋₄ alkoxy, F, Cl, Br, I, OH, NO₂ or NH₂ ;
 or R₁ and A are H and
 R₂ is (L)_a-(CH₂)_b-(T)_c-M wherein a, b, c, L, T, and M are as defined above ;
 Y is COR₃ or



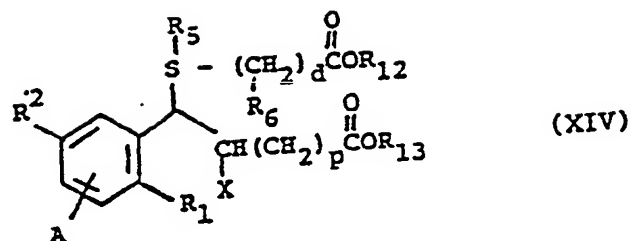
wherein
 R₃ is OH, NH₂, aryloxy, or C₁₋₈ alkoxy ;
 n is 0 or 1 ;
 p is 0, 1 or 2 ;
 X is H, OH, C₁₋₄ alkyl, C₁₋₄ alkoxy,
 or F ; and
 Z is COR₃, or tetrazolyl ;



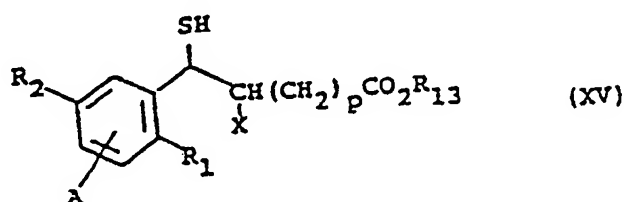
R₅ and R₆ are independently hydrogen or C₁₋₄ alkyl at any point when d is not 0 ;
 d is 0 to 6 ;
 W is a six membered aryl or heteroaryl ring selected from phenyl, pyridyl, or pyrimidyl, unsubstituted or
 substituted with B, C, or D ; or W is one of



wherein
 R₅ and R₆ are independently hydrogen or C₁₋₄ alkyl ; p is 0 to 6 ; V is H, C₁₋₄ alkyl, COR₃, SO₃H, SO₂H,
 SO₂NH₂, COCH₂OH, CHOHCH₂OH, or tetrazolyl, with R₃ as defined above ;
 C and D are independently selected from H, OH, F, Cl, Br, CF₃, C₁₋₄ alkyl, C₁₋₄ alkoxy, methylthio, trifluoromethylthio, NO₂, NH₂, NHC₁₋₄ alkyl, or C₁₋₄ alkylCO— ;
 or a pharmaceutically acceptable salt thereof, comprising
 a) reacting a strong base with a compound having the following structural formula (XIV)



wherein d is 2; X is OH; one of R_5 or R_6 adjacent to the ester group is H and the other is H or C_{1-4} alkyl; R_1 , R_2 , A, and p are as defined above and R_{12} and R_{13} are independently selected from C_{1-4} alkyl to yield a thiol represented by the following structural formula (XV)



wherein R_1 , R_2 , R_{13} , A, X, and p are defined as above for formula (XIV);

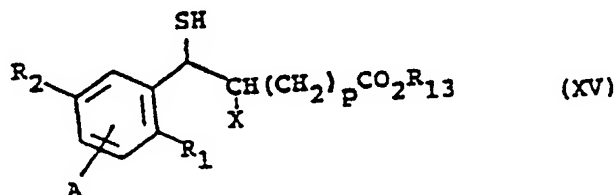
b) reacting the thiol of formula (XV) with an alkylating agent or Michael acceptor to yield a compound of Formula (I).

10. The process of Claim 9 wherein the alkylating agent is an alkyl halide.

11. The process of Claim 9 wherein the strong base is sodium hydride.

12. The process of Claim 9 wherein the Michael acceptor is an α , β -unsaturated carbonyl compound, or an alkyne containing a conjugated carbonyl group.

13. A compound represented by the following structural formula (XV):



wherein

R_1 is $(L)_a-(CH_2)_b-(T)_c-M$

a is 0 or 1

b is 3 to 14;

c is 0 or 1;

L and T are independently sulfur, oxygen or CH_2 ;

M is C_{1-4} alkyl, ethynyl, trifluoromethyl, isopropenyl, furanyl, thienyl, cyclohexyl or phenyl optionally mono-

substituted with Br, Cl, CF_3 , C_{1-4} alkoxy, C_{1-4} alkyl, methylthio, or trifluoromethylthio;

R_2 and A are independently selected from H, CF_3 , C_{1-4} alkyl, C_{1-4} alkoxy, F, Cl, Br, I, OH, NO_2 or NH_2 ;

or R_1 and A are H and

R_2 is $(L)_a-(CH_2)_b-(T)_c-M$ wherein a, b, c, L, T, and M are as defined above;

R_{13} is C_{1-8} alkyl;

p is 0, 1, or 2; and

X is OH.

14. The compound of claim 13 which is methyl 2-hydroxy-3-mercapto-3-[2-(8-phenyloctyl)phenyl]propionate.

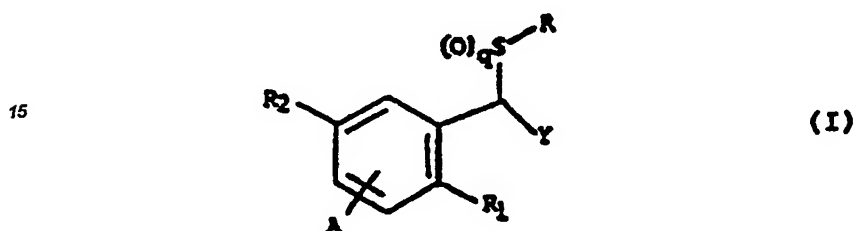
15. A compound which is methyl 2-hydroxy-3-(4-carbomethoxy-2-methoxyphenylmethylthio)-3-(8-phenyloctyl)phenyl]propionate;

methyl 2-hydroxy-3-(2-fluoro-4-carbomethoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionate ; or
methyl 2-methoxy-3-(4-carbomethoxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionate.

5 Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

10 1. Composé représenté par la formule développée (I) suivante :



20

dans laquelle

q est 0, 1 ou 2 ;

R₁ est (L)_a-(CH₂)_b-(T)_c-M ;

25

a est 0 ou 1 ;

b est 3 à 14 ;

c est 0 ou 1 ;

L et T sont indépendamment un atome de soufre ou d'oxygène ou un radical CH₂, sous réserve que L et T ne soient pas un atome de soufre lorsque q est 1 ou 2 ; et

30

M est un radical alkyle en C₁₋₄, éthynyle, trifluorométhyle, isopropényle, furannyle, thiényl, cyclohexyle ou phényle facultativement monosubstitué par Br, Cl, CF₃, alcoxy en C₁₋₄, alkyle en C₁₋₄, méthylthio ou trifluorométhylthio ;

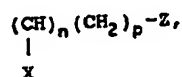
R₂ et A sont choisis indépendamment parmi H, CF₃, alkyle en

C₁₋₄, alcoxy en C₁₋₄, F, Cl, Br, I, OH, NO₂ ou NH₂ ; ou R₁ et A sont H et

35

R₂ est (L)_a-(CH₂)_b-(T)_c-M, où a, b, c, L, T et M sont tels que définis ci-dessus ;

Y est COR₃ ou



40

où

R₃ est OH, NH₂, aryloxy ou alcoxy en C₁₋₆ ;

n est 0 ou 1 ;

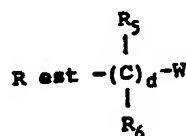
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p est 0, 1 ou 2 ;

X est H, OH, alkyle en C₁₋₄, alcoxy en C₁₋₄ ou F ; et

Z est COR₃ ou tétrazolyle ;

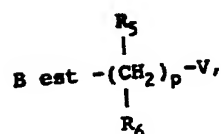
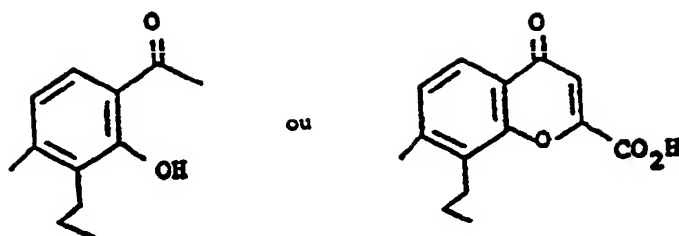
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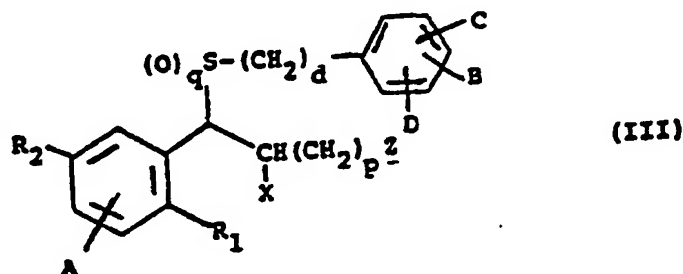
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R₅ et R₆ sont indépendamment un atome d'hydrogène ou un radical alkyle en C₁₋₄ lorsque d n'est pas 0 ; d est 0 à 6 ;

W est un cycle aryle ou hétéroaryle à six chaînons choisi parmi un radical phényle, pyridyle ou pyrimidyle non substitué ou substitué avec B, C ou D ; ou W est un de



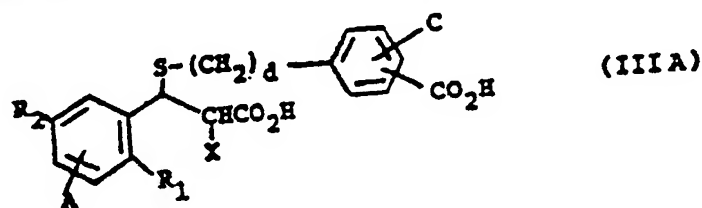
où
 R₅ et R₆ sont indépendamment un atome d'hydrogène ou un radical alkyle en C₁₋₄ ; p est 0 à 6 ; V est H,
 alkyle en C₁₋₄, COR₃, SO₃H, SO₂H, SO₂NH₂, COCH₂OH, CHOCH₂OH ou tétrazolyne, R₃ étant tel que
 défini ci-dessus ;
 C et D sont choisis indépendamment parmi H, OH, F, Cl, Br, CF₃, alkyle en C₁₋₄, alcoxy en C₁₋₄, méthylthio,
 trifluorométhylthio, NO₂, NH₂, NH-alkyle en C₁₋₄ ou (alkyl en C₁₋₄)CO— ;
 ou un sel pharmaceutiquement acceptable de celui-ci.
 2. Composé selon la revendication 1 représenté par la formule développée (III) suivante :



dans laquelle R₁, R₂, A, B, C, D, X, Z, p, q et d sont tels que définis dans la revendication 1 ou un sel pharmaceutiquement acceptable de celui-ci.

3. Composé selon la revendication 2, qui est l'acide 2-hydroxy-3-(4-hydroxyphénylthio)-3-[2-(8-phényloctyl)phényl] propionique.

4. Composé selon la revendication 2 représenté par la formule développée (IIIA) suivante



dans laquelle

X est OH, H ou OCH₃ ;

d est 0 ou 1 ; et

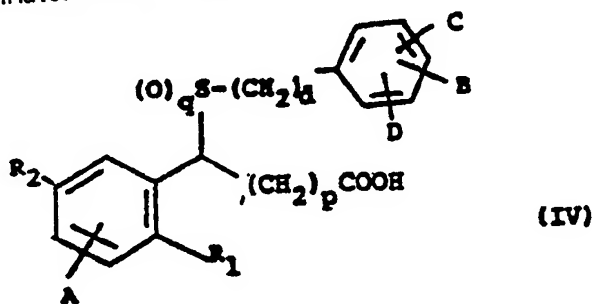
R₁, R₂, A et C sont tels que définis dans la revendication 2 ;

ou un sel pharmaceutiquement acceptable de celui-ci.

5. Composé selon la revendication 4, qui est :
 l'acide 2-hydroxy-3-(2-carboxyphénylthio)-3-[2-(8-phényloctyl)phényl]propionique ;

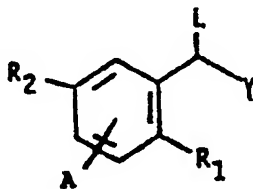
- l'acide 2(S)-hydroxy-3(R)-(2-carboxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionique ;
 l'acide 2(S)-hydroxy-3(R)-(3-carboxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionique ;
 l'acide 2-hydroxy-3-(3-carboxyphénylthio)-3-[2-(8-phényloctyl)phényl]propionique ;
 l'acide 2-hydroxy-3-(4-carboxyphénylthio)-3-(2-(8-phényloctyl)phényl]propionique ;
 l'acide 2-hydroxy-3-(4-carboxy-2-méthoxyphénylméthylthio)-3-(2-(8-phényloctyl)phényl]propionique ;
 l'acide 2-hydroxy-3-(4-carboxyphénylméthylthio)-3-(2-(8-phényloctyl)phényl]propionique ;
 l'acide 2-hydroxy-3-(2-fluoro-2-carboxyphénylméthylthio)-3-(2-(8-phényloctyl)phényl]propionique ;
 l'acide 2-méthoxy-3-(5-carboxyphénylthio)-3-(2-(8-phényloctyl)phényl]propionique ;
 l'acide 2-méthoxy-3-(5-carboxy-2-méthoxyphénylméthylthio)-3-(2-(8-phényloctyl)phényl]propionique ; ou
 l'acide 2-hydroxy-3-(5-carboxy-2-méthoxyphénylméthylthio)-3-(2-(8-phényloctyl)phényl]propionique.

6. Composé selon la revendication 1 représenté par la formule développée (IV) suivante :



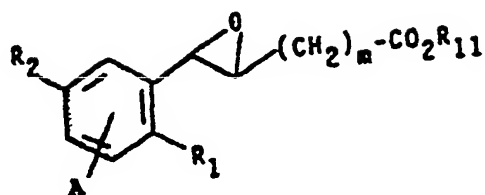
dans laquelle R_1 , R_2 , A, B, C, D, q et d sont tels que définis dans la revendication 1 et p est 1 ou 2.

7. Composé selon la revendication 6, qui est l'acide 3-(4-carboxy-2-méthoxyphénylméthylthio)-3-(2-(8-phényloctyl)phényl] propionique.
8. Composition pharmaceutique comprenant un véhicule ou diluant pharmaceutiques et une quantité efficace non toxique d'un composé selon la revendication 1.
9. Composition selon la revendication 8 sous une forme appropriée à l'administration orale, parentérale, locale ou par inhalation, dont le composant actif est l'acide 2-hydroxy-3-(4-carboxy-2-méthoxyphénylméthylthio)-3-(2-(8-phényloctyl)phényl] propionique ou l'acide 2-hydroxy-3-(2-fluoro-4-carboxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionique.
10. Composition pharmaceutique pour inhiber l'anaphylaxie respiratoire induite par un antigène comprenant un véhicule ou diluant pharmaceutiques et des quantités non toxiques, suffisantes pour produire cette inhibition, d'un composé selon la revendication 1 et d'un antagoniste des récepteurs H_1 à l'histamine.
11. Composé selon l'une quelconque des revendications 1 à 7 pour l'utilisation en thérapeutique.
12. Procédé pour la préparation d'un composé selon la revendication 1 de formule (I), qui comprend la réaction d'un thiol substitué convenablement protégé, RSH, où R est tel que défini dans la revendication 1, avec :
- (a) un composé de formule :

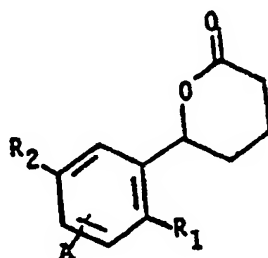


dans laquelle R_1 et R_2 sont tels que définis dans la revendication 1, L est un groupe labile choisi parmi chloro, bromo ou hydroxy ; Y est CO_2R_{10} ou $CH(R_{12})CO_2R_{10}$, où R_{10} est un groupe protecteur ester et R_{12} est un atome d'hydrogène ou un radical méthyle, méthoxy ou fluoro, pour former des composés dans lesquels Y est CO_2H ou $CH(R_{12})CO_2H$;

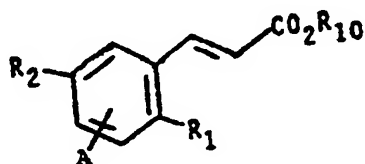
(b) un composé de formule :



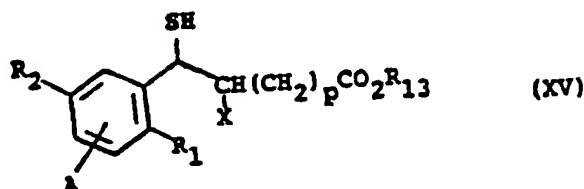
dans laquelle R_1 , R_2 et m sont tels que définis dans la revendication 1 et R_{11} est un radical alkyle inférieur,
pour former des composés dans lesquels Y est $CH(OH)(CH_2)_mCO_2H$;
(c) un composé de formule :



dans laquelle R_1 et R_2 sont tels que définis dans la revendication 1, pour former des composés dans les-
quels Y est $(CH_2)_3CO_2H$; et
(d) un composé de formule :



dans laquelle R_1 et R_2 sont tels que définis dans la revendication 1 et R_{10} est un groupe protecteur ester,
pour former des composés dans lesquels Y est CH_2CO_2H ;
suivie de l'élimination de tout groupe protecteur, éventuellement du dédoublement de tout mélange dias-
téro-isomère de composés et facultativement la formation d'un sel pharmaceutiquement acceptable.
13. Composé représenté par la formule développée (XV) suivante :



dans laquelle

R_1 est $(L)_a(CH_2)_b(T)_cM$

a est 0 ou 1 ;

b est 3 à 14 ;

c est 0 ou 1 ;

L et T sont indépendamment un atome de soufre ou d'oxygène ou un radical CH_2 ;

M est un radical alkyle en C_{1-4} , éthynyle, trifluorométhyle, isopropényle, furannyle, thiényl, cyclohexyle
ou phényle facultativement monosubstitué avec Br , Cl , CF_3 , alcoxy en C_{1-4} , alkyle en C_{1-4} , méthylthio ou
trifluorométhylthio ;

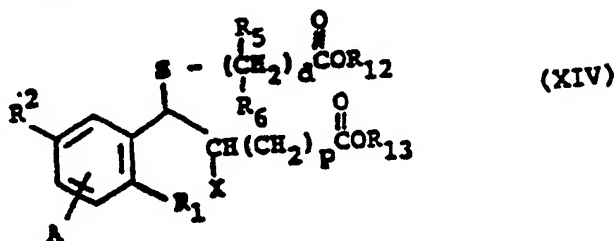
R_2 et A sont indépendamment choisis parmi H , CF_3 , alkyle en C_{1-4} , alcoxy en C_{1-4} , F , Cl , Br , I , OH , NO_2

ou NH_2 ;
 ou R_1 et A sont H et
 R_2 est $(\text{L})\text{a}-(\text{CH}_2)_b-(\text{T})_c-\text{M}$, où a , b , c , L , T et M sont tels que définis ci-dessus ;
 R_{13} est un radical alkyle en C_{1-8} ;
 p est 0, 1 ou 2 ; et
 X est OH .

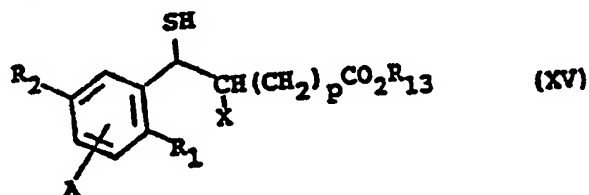
14. Composé selon la revendication 13, qui est le 2-hydroxy-3-mercapto-3-[2-(8-phényloctyl)phényl]propionate de méthyle.

15. Procédé pour la préparation d'un composé selon la revendication 1 comprenant :

a) la réaction d'une base forte avec un composé répondant à la formule développée (XIV) suivante



dans laquelle d est 2 ; X est OH ; un de R_5 ou R_6 adjacent au groupe ester est H et l'autre est H ou un radical alkyle en C_{1-4} ; R_1 , R_2 , A et p sont tels que définis dans la revendication 1 et R_{12} et R_{13} sont indépendamment un alkyle en C_{1-4} , pour former un thiol représenté par la formule développée (XV) suivante



dans laquelle R_1 , R_2 , R_{13} , A , X et p sont tels que définis ci-dessus pour la formule (XIV) ;

b) la réaction du thiol de formule (XV) avec un agent d'alkylation ou un accepteur de Michael, pour former un composé de formule (I).

16. Procédé selon la revendication 15, dans lequel l'agent d'alkylation est un halogénure d'alkyle et la base forte est l'hydruure de sodium.

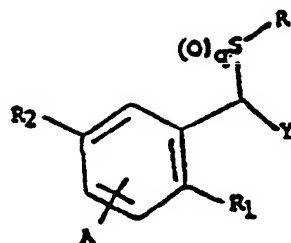
17. Procédé selon la revendication 15, dans lequel l'accepteur de Michael est un composé carbonylé α , β -insaturé ou un alcynes contenant un groupe carbonylé conjugué.

18. Composé selon la revendication 2, qui est le 2-hydroxy-3-(4-carbométhoxy-2-méthoxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionate de méthyle ;
 le 2-hydroxy-3-(2-fluoro-4-carbométhoxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionate de méthyle ;
 ou
 le 2-méthoxy-3-(4-carbométhoxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionate de méthyle.

19. Composé selon l'une quelconque des revendications 1 à 7 pour l'utilisation dans le traitement de maladies dont les leucotriènes sont un facteur.

Revendications pour l'Etat contractant suivant : ES

1. Procédé pour la préparation de composés représentés par la formule développée (I) suivante :



(I)

dans laquelle

q est 0, 1 ou 2 ;

R_1 est $(L)_a-(CH_2)_b-(T)_c-M$;

a est 0 ou 1 ;

b est 3 à 14 ;

c est 0 ou 1 ;

L et T sont indépendamment un atome de soufre ou d'oxygène ou un radical CH_2 , sous réserve que L et T ne soient pas un atome de soufre lorsque q est 1 ou 2 ;

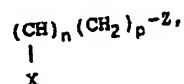
M est un radical alkyle en C_{1-4} , éthynyle, trifluorométhyle, isopropényle, furannyle, thiényl, cyclohexyle ou phényle facultativement monosubstitué par Br, Cl, CF_3 , alcoxy en C_{1-4} , alkyle en C_{1-4} , méthylthio ou trifluorométhylthio ;

R_2 et A sont choisis indépendamment parmi H, CF_3 , alkyle en C_{1-4} , alcoxy en C_{1-4} , F, Cl, Br, I, OH, NO_2 ou NH_2 ;

ou R_1 et A sont H et

R_2 est $(L)_a-(CH_2)_b-(T)_c-M$, où a, b, c, L, T et M sont tels que définis ci-dessus ;

Y est COR_3 ou



où

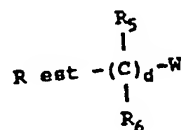
R_3 est OH, NH_2 , aryloxy ou alcoxy en C_{1-6} ;

n est 0 ou 1 ;

p est 0, 1 ou 2 ;

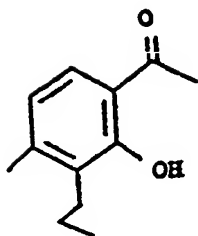
X est H, OH, alkyle en C_{1-4} , alcoxy en C_{1-4} ou F ; et

Z est COR_3 ou tétrazolyne ;

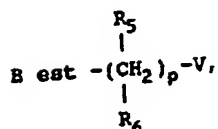
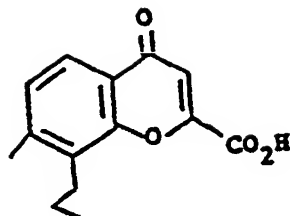


R_5 et R_6 sont indépendamment un atome d'hydrogène ou un radical alkyle en C_{1-4} lorsque d n'est pas 0 ; d est 0 à 6 ;

W est un cycle aryle ou hétéroaryle à six chaînons choisi parmi un radical phényle, pyridyle ou pyrimidyle non substitué ou substitué avec B, C ou D ; ou W est un de



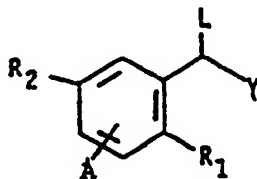
ou



où
 R_5 et R_6 sont indépendamment un atome d'hydrogène ou un radical alkyle en C_{1-4} ; p est 0 à 6; V est H,
 alkyle en C_{1-4} , COR_3 , SO_3H , SO_2H , SO_2NH_2 , COCH_2OH , CHOHCH_2OH ou tétrazole, R_3 étant tel que
 défini ci-dessus;

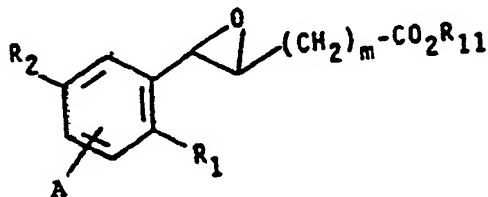
C et D sont choisis indépendamment parmi H, OH, F, Cl, Br, CF_3 , alkyle en C_{1-4} , alcoxy en C_{1-4} , méthylthio,
 trifluorométhylthio, NO_2 , NH_2 , NH-alkyle en C_{1-4} ou (alkyl en C_{1-4})CO—;
 ou leurs sels pharmaceutiquement acceptables, qui comprend la réaction d'un thiol substitué convenable-
 ment protégé, RSH , où R est tel que défini ci-dessus, avec:

(a) un composé de formule :



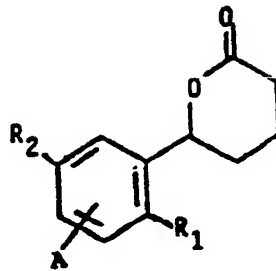
dans laquelle R_1 et R_2 sont tels que définis dans la revendication 1, L est un groupe labile choisi parmi
 chloro, bromo ou hydroxy; Y est CO_2R_{10} ou $\text{CH}(\text{R}_{12})\text{CO}_2\text{R}_{10}$, où R_{10} est un groupe protecteur ester et R_{12}
 est un atome d'hydrogène ou un radical méthyle ou fluoro, pour former des composés dans lesquels Y est
 CO_2H ou $\text{CH}(\text{R}_{12})\text{CO}_2\text{H}$;

(b) un composé de formule :

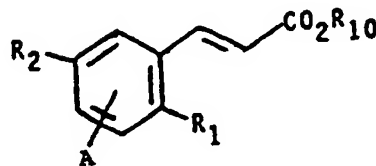


dans laquelle R_1 , R_2 et m sont tels que définis ci-dessus et R_{11} est un radical alkyle inférieur, pour former
 des composés dans lesquels Y est $\text{CH}(\text{OH})(\text{CH}_2)_m\text{CO}_2\text{H}$;

(c) un composé de formule :



dans laquelle R_1 et R_2 sont tels que définis ci-dessus, pour former des composés dans lesquels Y est $(CH_2)_3CO_2H$; et
(d) un composé de formule :



dans laquelle R_1 et R_2 sont tels que définis ci-dessus et R_{10} est un groupe protecteur ester, pour former des composés dans lesquels Y est CH_2CO_2H ;

suivie de l'élimination de tout groupe protecteur, éventuellement du dédoublement de tout mélange diastéréo-isomère de composés et facultativement la formation d'un sel pharmaceutiquement acceptable.

2. Procédé selon la revendication 1(b), dans lequel on fait réagir le trans-3-[2-(8-phényloctyl)phényl]-2,3-époxypropionate de méthyle et le 4-mercaptométhyl-3-méthoxybenzoate de méthyle pour obtenir l'acide 2-hydroxy-3-(4-carboxy-2-méthoxyphénylméthylthio)-3[2-(8-phényloctyl)phényl]propionique.

3. Procédé selon la revendication 1(b), dans lequel on fait réagir le trans-3-[2-(8-phényloctyl)phényl]-2,3-époxypropionate de méthyle et l'acide p-mercaptobenzoïque pour obtenir le 2-hydroxy-3-(4-carboxyméthoxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionate de méthyle, que l'on fait ensuite réagir avec l'hydruide de sodium et l'iodométhane pour obtenir l'acide 2-méthoxy-3-(4-carboxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionique.

4. Procédé selon la revendication 1(b), dans lequel on fait réagir le trans-3-[2-(8-phényloctyl)phényl]-2,3-époxypropionate de méthyle et le 2-fluoro-4-mercaptométhylbenzoate de méthyle pour obtenir l'acide 2-hydroxy-3-(2-fluoro-4-carboxyphénylméthylthio)-3[2-(8-phényloctyl)phényl]propionique.

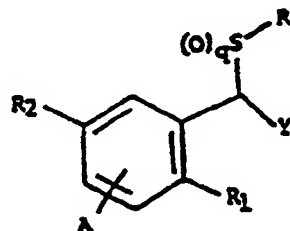
5. Procédé selon la revendication 3, dans lequel on dédouble le mélange érythro de diastéréo-isomères pour obtenir l'acide 2(S)-méthoxy-3(R)-(4-carboxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionique.

6. Procédé selon les revendications 2, 3 ou 4, dans lequel le produit est transformé en son sel disodique.

7. Procédé pour la préparation d'une composition pharmaceutique comprenant le mélange d'un véhicule ou diluant pharmaceutiques et d'un composé de formule (I), tel que défini dans la revendication 1.

8. Procédé pour la préparation d'une composition pharmaceutique comprenant le mélange d'un véhicule ou diluant pharmaceutiques, d'un composé de formule (I), tel que défini dans la revendication 1, et d'un antagoniste des récepteurs H_1 à l'histamine.

9. Procédé pour la préparation d'un composé représenté par la formule développée (I) suivante :



(I)

dans laquelle

q est 0, 1 ou 2 ;

R_1 est $(L)_a-(CH_2)_b-(T)_c-M$;

a est 0 ou 1 ;

b est 3 à 14 ;

c est 0 ou 1 ;

L et T sont indépendamment un atome de soufre ou d'oxygène ou un radical CH_2 , sous réserve que L et T ne soient pas un atome de soufre lorsque q est 1 ou 2 ;

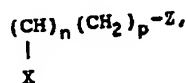
M est un radical alkyle en C_{1-4} , éthynyle, trifluorométhyle, isopropényle, furannyle, thiényl, cyclohexyle ou phényle facultativement monosubstitué par Br, Cl, CF_3 , alcoxy en C_{1-4} , alkyle en C_{1-4} , méthylthio ou trifluorométhylthio ;

R_2 et A sont choisis indépendamment parmi H, CF_3 , alkyle en C_{1-4} , alcoxy en C_{1-4} , F, Cl, Br, I, OH, NO_2 ou NH_2 ;

ou R_1 et A sont H et

R_2 est $(L)_a-(CH_2)_b-(T)_c-M$, où a, b, c, L, T et M sont tels que définis ci-dessus ;

Y est COR_3 ou



où

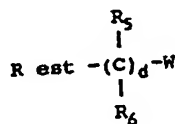
R_3 est OH, NH_2 , aryloxy ou alcoxy en C_{1-8} ;

n est 0 ou 1 ;

p est 0, 1 ou 2 ;

X est H, OH, alkyle en C_{1-4} , alcoxy en C_{1-4} ou F ; et

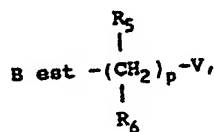
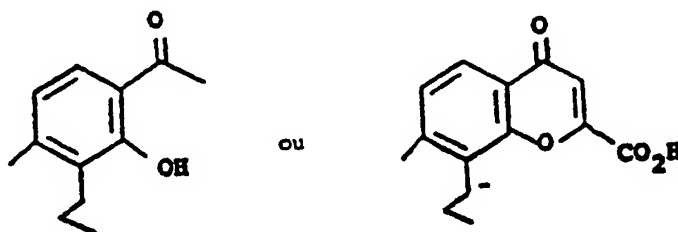
Z est COR_3 ou tétrazolye ;



R_5 et R_6 sont indépendamment un atome d'hydrogène ou un radical alkyle en C_{1-4} lorsque d n'est pas 0 ;

d est 0 à 6 ;

W est un cycle aryle ou hétéroaryle à six chaînons choisi parmi un radical phényle, pyridyle ou pyrimidyle non substitué ou substitué avec B, C ou D ; ou W est un de



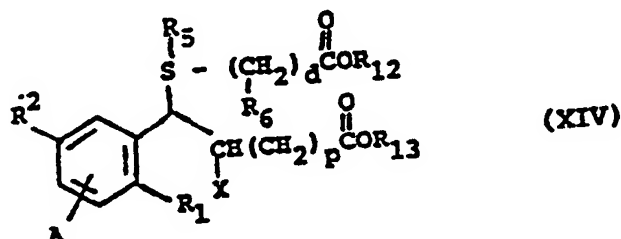
où

R_5 et R_6 sont indépendamment un atome d'hydrogène ou un radical alkyle en C_{1-4} ; p est 0 à 6 ; V est H, alkyle en C_{1-4} , COR_3 , SO_3H , SO_2H , SO_2NH_2 , $COCH_2OH$, $CHOHCH_2OH$ ou tétrazolye, R_3 étant tel que défini ci-dessus ;

C et D sont choisis indépendamment parmi H, OH, F, Cl, Br, CF₃, alkyle en C₁₋₄, alcoxy en C₁₋₄, méthylthio, trifluorométhylthio, NO₂, NH₂, NH-alkyle en C₁₋₄ ou (alkyl en C₁₋₄)CO— ;
ou un sel pharmaceutiquement acceptable de celui-ci, comprenant
a) la réaction d'une base forte avec un composé répondant à la formule développée (XIV) suivante

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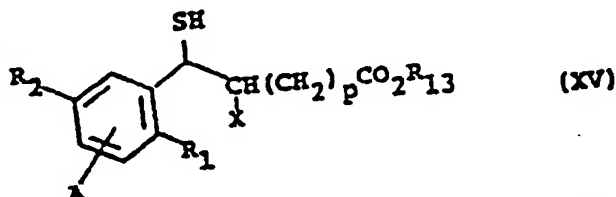


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dans laquelle d est 2 ; X est OH ; un de R₅ ou R₆ adjacent au groupe ester est H et l'autre est H ou un radical alkyle en C₁₋₄ ; R₁, R₂, A et p sont tels que définis ci-dessus et R₁₂ et R₁₃ sont indépendamment un alkyle en C₁₋₄, pour former un thiol représenté par la formule développée (XV) suivante

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dans laquelle R₁, R₂, R₁₃, A, X et p sont tels que définis ci-dessus pour la formule (XIV) ;

b) la réaction du thiol de formule (XV) avec un agent d'alkylation ou un accepteur de Michael, pour former un composé de formule (I).

10. Procédé selon la revendication 9, dans lequel l'agent d'alkylation est un halogénure d'alkyle.

11. Procédé selon la revendication 9, dans lequel la base forte est l'hydrure de sodium.

12. Procédé selon la revendication 9, dans lequel l'accepteur de Michael est un composé carbonyle α, β-insaturé ou un alcyne contenant un groupe carbonyle conjugué.

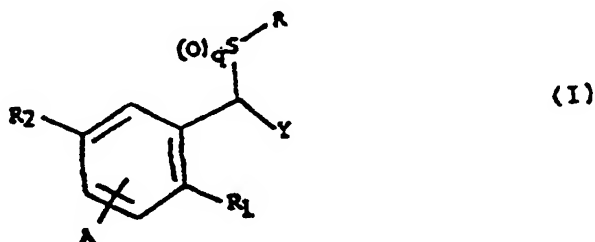
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Revendications pour l'Etat contractant suivant : GR

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1. Procédé pour la préparation des composés représentés par la formule développée (I) suivante :

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dans laquelle

q est 0, 1 ou 2 ;

R₁ est (L)_a-(CH₂)_b-(T)_c-M ;

a est 0 ou 1 ;

b est 3 à 14 ;

c est 0 ou 1 ;

L et T sont indépendamment un atome de soufre ou d'oxygène ou un radical CH₂, sous réserve que L et T ne soient pas un atome de soufre lorsque q est 1 ou 2 ;

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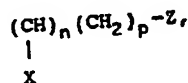
M est un radical alkyle en C₁₋₄, éthylnyle, trifluorométhyle, isopropényle, furannyle, thiényne, cyclohexyle ou phényle facultativement monosubstitué par Br, Cl, CF₃, alcoxy en C₁₋₄, alkyle en C₁₋₄, méthylthio ou trifluorométhylthio ;

R₂ et A sont choisis indépendamment parmi H, CF₃, alkyle en C₁₋₄, alcoxy en C₁₋₄, F, Cl, Br, I, OH, NO₂ ou NH₂ ;

ou R₁ et A sont H et

R₂ est (L)_a-(CH₂)_b-(T)_c-M, où a, b, c, L, T et M sont tels que définis ci-dessus ;

Y est COR₃ ou



où

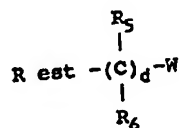
R₃ est OH, NH₂, aryloxy ou alcoxy en C₁₋₆ ;

n est 0 ou 1 ;

p est 0, 1 ou 2 ;

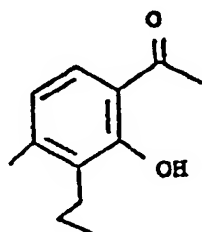
X est H, OH, alkyle en C₁₋₄, alcoxy en C₁₋₄ ou F ; et

Z est COR₃ ou tétrazolyne ;

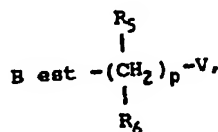
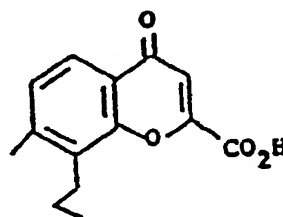


R₅ et R₆ sont indépendamment un atome d'hydrogène ou un radical alkyle en C₁₋₄ lorsque d n'est pas 0 ; d est 0 à 6 ;

W est un cycle aryle ou hétéroaryle à six chaînons choisi parmi un radical phényle, pyridyle ou pyrimidyle non substitué ou substitué avec B, C ou D ; ou W est un de



ou



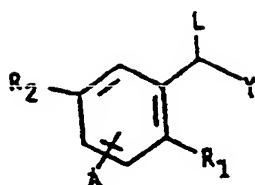
où

R₅ et R₆ sont indépendamment un atome d'hydrogène ou un radical alkyle en C₁₋₄ ; p est 0 à 6 ; V est H, alkyle en C₁₋₄, COR₃, SO₃H, SO₂H, SO₂NH₂, COCH₂OH, CHOHCH₂OH ou tétrazolyne, R₃ étant tel que défini ci-dessus ;

C et D sont choisis indépendamment parmi H, OH, F, Cl, Br, CF₃, alkyle en C₁₋₄, alcoxy en C₁₋₄, méthylthio, trifluorométhylthio, NO₂, NH₂, NH-alkyle en C₁₋₄ ou (alkyl en C₁₋₄)CO— ;

ou leurs sels pharmaceutiquement acceptables, qui comprend la réaction d'un thiol substitué convenablement protégé, RSH, où R est tel que défini ci-dessus avec :

(a) un composé de formule :

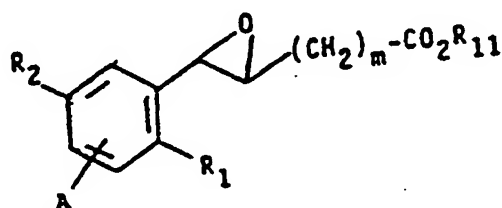


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dans laquelle R_1 et R_2 sont tels que définis dans la revendication 1, L est un groupe labile choisi parmi chloro, bromo ou hydroxy ; Y est CO_2R_{10} ou $\text{CH}(\text{R}_{12})\text{CO}_2\text{R}_{10}$, où R_{10} est un groupe protecteur ester et R_{12} est un atome d'hydrogène ou un radical méthyle ou fluoro, pour former des composés dans lesquels Y est CO_2H ou $\text{CH}(\text{R}_{12})\text{CO}_2\text{H}$;
 (b) un composé de formule :

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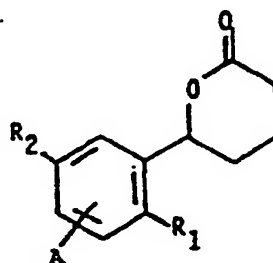


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dans laquelle R_1 , R_2 et m sont tels que définis ci-dessus et R_{11} est un radical alkyle inférieur, pour former des composés dans lesquels Y est $\text{CH}(\text{OH})(\text{CH}_2)_m\text{CO}_2\text{H}$;
 (c) un composé de formule :

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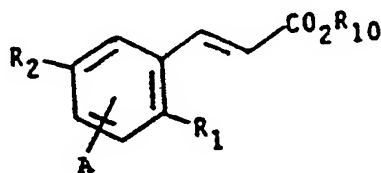


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dans laquelle R_1 et R_2 sont tels que définis ci-dessus, pour former des composés dans lesquels Y est $(\text{CH}_2)_3\text{CO}_2\text{H}$; et
 (d) un composé de formule :

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dans laquelle R_1 et R_2 sont tels que définis ci-dessus et R_{10} est un groupe protecteur ester, pour former des composés dans lesquels Y est $\text{CH}_2\text{CO}_2\text{H}$;
 suivie de l'élimination de tout groupe protecteur, éventuellement du dédoublement de tout mélange diastéréo-isomère de composés et facultativement la formation d'un sel pharmaceutiquement acceptable.
 2. Procédé selon la revendication 1(b), dans lequel on fait réagir le trans-3-[2-(8-phényloctyl)phényl]-2,3-époxypropionate de méthyle et le 4-mercaptométhyl-3-méthoxybenzoate de méthyle pour obtenir l'acide 2-hydroxy-3-(4-carboxy-2-méthoxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionique.
 3. Procédé selon la revendication 1(b), dans lequel on fait réagir le trans-3-[2-(8-phényloctyl)phényl]-2,3-époxypropionate de méthyle et l'acide p-mercaptobenzoïque pour obtenir le 2-hydroxy-3(4-carbométhoxyphé-

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nylthio)-3-[2-(8-phényloctyl)phényl]propionate de méthyle, que l'on fait ensuite réagir avec l'hydrure de sodium et l'iodométhane pour obtenir l'acide 2-méthoxy-3-(4-carboxyphénylthio)-3-[2-(8-phényloctyl)phényl]propionique.

4. Procédé selon la revendication 1(b), dans lequel on fait réagir le trans-3-[2-(8-phényloctyl)phényl]-2,3-époxypropionate de méthyle et le 2-fluoro-4-mercaptométhylbenzoate de méthyle pour obtenir l'acide 2-hydroxy-3-(2-fluoro-4-carboxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionique.

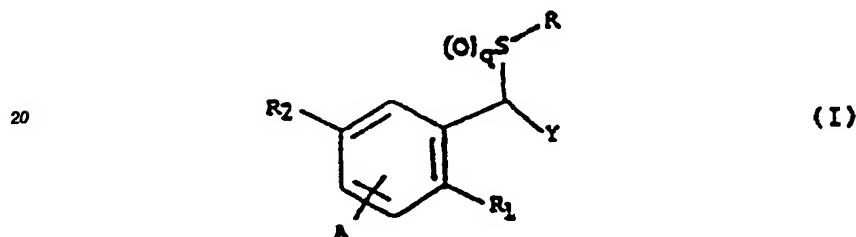
5. Procédé selon la revendication 3, dans lequel on dédouble le mélange érythro de diastéréo-isomères pour obtenir l'acide 2(S)-méthoxy-3(R)-(4-carboxyphénylthio)-3-[2-(8-phényloctyl)phényl]propionique.

6. Procédé selon les revendications 2, 3 ou 4, dans lequel le produit est transformé en son sel disodique.

7. Procédé pour la préparation d'une composition pharmaceutique comprenant le mélange d'un véhicule ou diluant pharmaceutiques et d'un composé de formule (I), tel que défini dans la revendication 1.

8. Procédé pour la préparation d'une composition pharmaceutique comprenant le mélange d'un véhicule ou diluant pharmaceutiques, d'un composé de formule (I), tel que défini dans la revendication 1, et d'un antagoniste des récepteurs H_1 à l'histamine.

9. Procédé pour la préparation d'un composé représenté par la formule développée (I) suivante :



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dans laquelle

q est 0, 1 ou 2 ;

R_1 est $(L)_a-(CH_2)_b-(T)_c-M$;

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a est 0 ou 1 ;

b est 3 à 14 ;

c est 0 ou 1 ;

L et T sont indépendamment un atome de soufre ou d'oxygène ou un radical CH_2 , sous réserve que L et T ne soient pas un atome de soufre lorsque q est 1 ou 2 ; et

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M est un radical alkyle en C_{1-4} , éthynyle, trifluorométhyle, isopropényle, furannyle, thiényl, cyclohexyle ou phényle facultativement monosubstitué par Br, Cl, CF_3 , alcoxy en C_{1-4} , alkyle en C_{1-4} , méthylthio ou trifluorométhylthio ;

R_2 et A sont choisis indépendamment parmi H, CF_3 , alkyle en C_{1-4} , alcoxy en C_{1-4} , F, Cl, Br, I, OH, NO_2 ou NH_2 ;

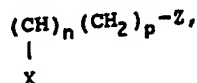
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ou R_1 et A sont H et

R_2 est $(L)_a-(CH_2)_b-(T)_c-M$, où a, b, c, L, T et M sont tels que définis ci-dessus ;

Y est COR_3 ou

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où

R_3 est OH, NH_2 , aryloxy ou alcoxy en C_{1-8} ;

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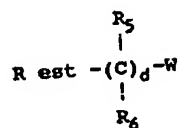
n est 0 ou 1 ;

p est 0, 1 ou 2 ;

X est H, OH, alkyle en C_{1-4} , alcoxy en C_{1-4} ou F ; et

Z est COR_3 ou tétrazolyle ;

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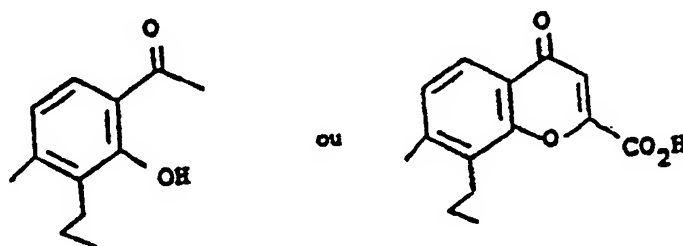
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R_5 et R_6 sont indépendamment un atome d'hydrogène ou un radical alkyle en C_{1-4} lorsque d n'est pas 0 ;
 d est 0 à 6 ;

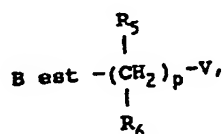
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W est un cycle aryle ou hétéroaryle à six chaînons choisi parmi un radical phényle, pyridyle ou pyrimidyle
 non substitué ou substitué avec B, C ou D ; ou W est un de

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où
 R_5 et R_6 sont indépendamment un atome d'hydrogène ou un radical alkyle en C_{1-4} ; p est 0 à 6 ; V est H,
 alkyle en C_{1-4} , COR_3 , SO_3H , SO_2NH_2 , $COCH_2OH$, $CHOHCH_2OH$ ou tétrazolye, R_3 étant tel que

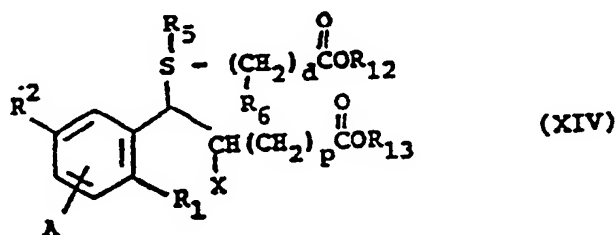
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défini ci-dessus ;
 C et D sont choisis indépendamment parmi H, OH, F, Cl, Br, CF_3 , alkyle en C_{1-4} , alcoxy en C_{1-4} , méthylthio,
 trifluorométhylthio, NO_2 , NH_2 , NH-alkyle en C_{1-4} ou (alkyl en C_{1-4})CO— ;
 ou un sel pharmaceutiquement acceptable de celui-ci, comprenant

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a) la réaction d'une base forte avec un composé répondant à la formule développée (XIV) suivante

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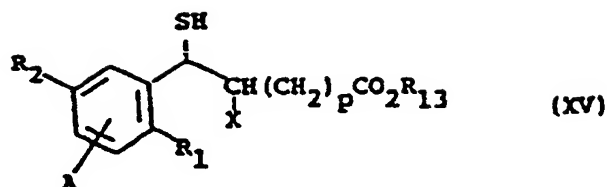


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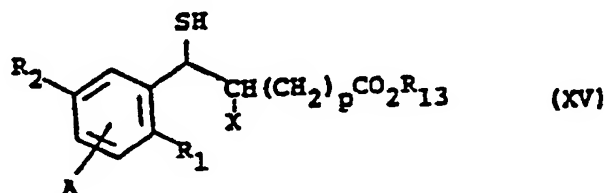
dans laquelle d est 2 ; X est OH ; un de R_5 ou R_6 adjacent au groupe ester est H et l'autre est H ou un
 radical alkyle en C_{1-4} ; R_1 , R_2 , A et p sont tels que définis ci-dessus et R_{12} et R_{13} sont indépendamment
 un alkyle en C_{1-4} , pour former un thiol représenté par la formule développée (XV) suivante

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- 10 dans laquelle R_1 , R_2 , R_{13} , A, X et p sont tels que définis ci-dessus pour la formule (XIV) ;
 b) la réaction du thiol de formule (XV) avec un agent d'alkylation ou un accepteur de Michael, pour former un composé de formule (I).
 10. Procédé selon la revendication 9, dans lequel l'agent d'alkylation est un halogénure d'alkyle.
 11. Procédé selon la revendication 9, dans lequel la base forte est l'hydrure de sodium.
 12. Procédé selon la revendication 9, dans lequel l'accepteur de Michael est un composé carbonyle α , β -
 15 Insaturé ou un alcyne contenant un groupe carbonyle conjugué.
 13. Composé représenté par la formule développée (XV) suivante :



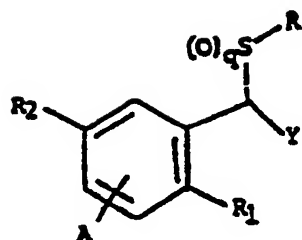
dans laquelle

- R_1 est $(L)_a-(CH_2)_b-(T)_c-M$
 a est 0 ou 1 ;
 30 b est 3 à 14 ;
 c est 0 ou 1 ;
 L et T sont indépendamment un atome de soufre ou d'oxygène ou un radical CH_2 ;
 M est un radical alkyle en C_{1-4} , éthynyle, trifluorométhyle, isopropényle, furannyle, thiényne, cyclohexyle ou phényle facultativement monosubstitué avec Br, Cl, CF_3 , alcoxy en C_{1-4} , alkyle en C_{1-4} , méthylthio ou trifluorométhylthio ;
 35 R_2 et A sont indépendamment choisis parmi H, CF_3 , alkyle en C_{1-4} , alcoxy en C_{1-4} , F, Cl, Br, I, OH, NO_2 ou NH_2 ;
 ou R_1 et A sont H et
 R_2 est $(L)_a-(CH_2)_b-(T)_c-M$, où a, b, c, L, T et M sont tels que définis ci-dessus ;
 40 R_{13} est un radical alkyle en C_{1-8} ;
 p est 0, 1 ou 2 ; et
 X est OH.
 14. Composé selon la revendication 13, qui est le 2-hydroxy-3-mercapto-3-[2-(8-phényloctyl)phényl]propionate de méthyle.
 15. Composé qui est le 2-hydroxy-3-(4-carbométhoxy-2-méthoxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionate de méthyle ;
 45 le 2-hydroxy-3-(2-fluoro-4-carbométhoxyphénylméthylthio)-3-[2-(8-phényloctyl)phényl]propionate de méthyle ;
 ou
 le 2-méthoxy-3-(4-carbométhoxyphénylthio)-3-[2-(8-phényloctyl)phényl]propionate de méthyle.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

- 55 1. Verbindung der folgenden Strukturformel (I)



(I)

in der

q 0, 1 oder 2 ist ;

R₁ (L)_a-(CH₂)_b-(T)_c-M bedeutet,

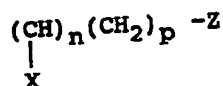
a 0 oder 1 ist ;

b 3 bis 14 ist ;

c 0 oder 1 ist ;

L und T unabhängig Schwefel, Sauerstoff oder CH₂ bedeuten, mit der Maßgabe, daß L und T nicht Schwefel sind, wenn q 1 oder 2 ist ; undM C₁₋₄-Alkyl, Ethinyl, Trifluormethyl, Isopropenyl, Furanyl, Thienyl, Cyclohexyl oder Phenyl, gegebenenfalls monosubstituiert mit Br, Cl, CF₃, C₁₋₄-Alkoxy, C₁₋₄-Alkyl, Methylthio oder Trifluormethylthio, bedeutet ;R₂ und A unabhängig ausgewählt sind aus H, CF₃, C₁₋₄-Alkyl, C₁₋₄-Alkoxy, F, Cl, Br, I, OH, NO₂ oder NH₂ ;oder R₁ und A H sind undR₂ (L)_a-(CH₂)_b-(T)_c-M bedeutet, wobei a, b, c, L, T und

M wie vorstehend definiert sind ;

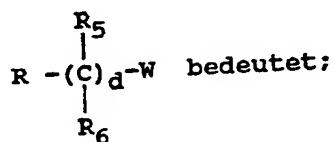
Y COR₃ oder

bedeutet, wobei

R₃ OH, NH₂, Aryloxy oder C₁₋₆-Alkoxy darstellt ;

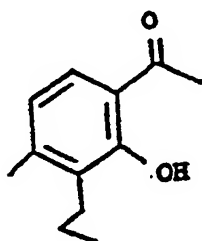
n 0 oder 1 ist ;

p 0, 1 oder 2 ist ;

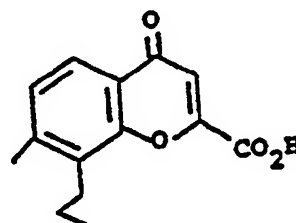
X H, OH, C₁₋₄-Alkyl, C₁₋₄-Alkoxy oder F bedeutet ; undZ COR₃ oder Tetrazolyl bedeutet ;R₅ und R₆ unabhängig Wasserstoff oder C₁₋₄-Alkyl in jedem Fall bedeuten, wenn d nicht 0 ist ;

d 0 bis 6 ist ;

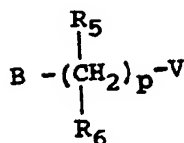
W einen sechsgliedrigen Aryl- oder Heteroaryling, ausgewählt aus Phenyl, Pyridyl oder Pyrimidyl, unsubstituiert oder substituiert mit B, C oder D bedeutet ; oder W eine der Formeln



oder



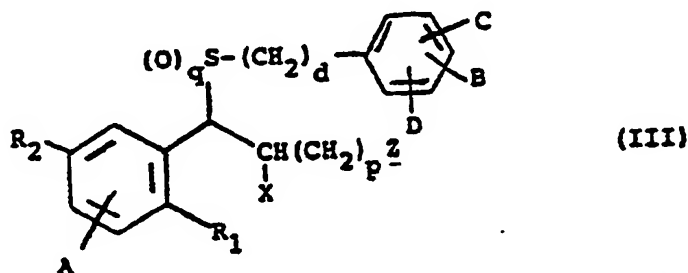
darstellt,



bedeutet, wobei

R_5 und R_6 unabhängig Wasserstoff oder C_{1-4} -Alkyl darstellen, p 0 bis 6 ist; V H, C_{1-4} -Alkyl, COR_3 , SO_3H , SO_2H , SO_2NH_2 , COCH_2OH , CHOHCH_2OH oder Tetrazolyl bedeutet, wobei R_3 wie vorstehend definiert ist; C und D unabhängig ausgewählt sind aus H, OH, F, Cl, Br, CF_3 , C_{1-4} -Alkyl, C_{1-4} -Alkoxy, Methylthio, Trifluormethylthio, NO_2 , NH_2 , NHC_{1-4} -Alkyl oder C_{1-4} -AlkylCO—; oder ein pharmazeutisch verträgliches Salz davon.

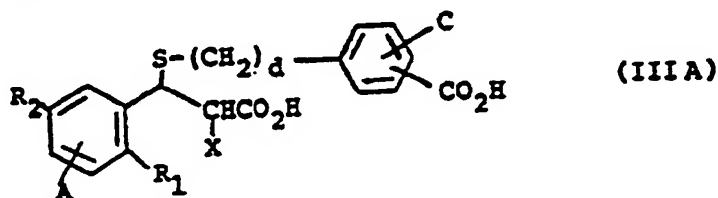
2. Verbindung nach Anspruch 1 der folgenden Strukturformel (III)



in der R_1 , R_2 , A, B, C, D, X, Z, p, q und d wie in Anspruch 1 definiert sind, oder ein pharmazeutisch verträgliches Salz davon.

3. Verbindung nach Anspruch 2, nämlich 2-Hydroxy-3-(4-hydroxyphenylthio)-3-[2-(8-phenyloctyl)-phenyl]-propionsäure.

4. Verbindung nach Anspruch 2 der folgenden Strukturformel (IIIA),



in der

X OH, H oder OCH_3 bedeutet;

d 0 oder 1 ist; und

R_1 , R_2 , A und C wie in Anspruch 2 definiert sind;

oder ein pharmazeutisch verträgliches Salz davon.

5. Verbindung nach Anspruch 4, nämlich

2-Hydroxy-3-(2-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure;

2(S)-Hydroxy-3(R)-(2-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure;

2(S)-Hydroxy-3(R)-(3-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure;

2-Hydroxy-3-(3-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure;

2-Hydroxy-3-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure;

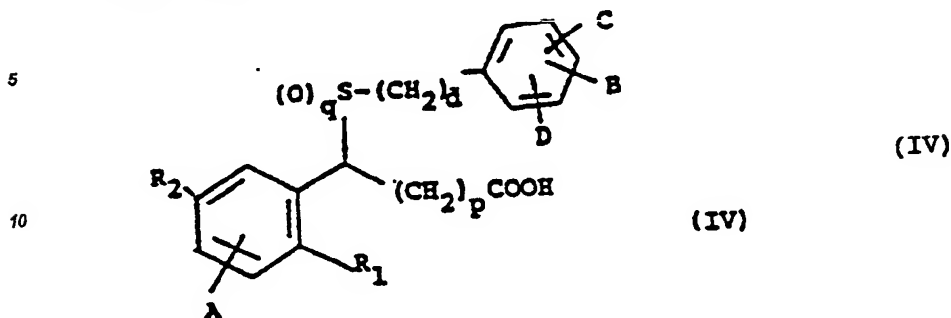
2-Hydroxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure;

2-Hydroxy-3-(4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure;

2-Hydroxy-3-(2-fluor-4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure;

2-Methoxy-3-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure oder 2-Methoxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure oder

2-Hydroxy-3-(5-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure.
6. Verbindung nach Anspruch 1 der folgenden Strukturformel (IV)



15 in der R₁, R₂, A, B, C, D, q und d wie in Anspruch 1 definiert sind und p 1 oder 2 ist.

7. Verbindung nach Anspruch 6, nämlich 3-(4-Carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]-propionsäure.

8. Arzneimittel, umfassend einen pharmazeutischen Träger oder ein Verdünnungsmittel und eine nichtto-

20 xische wirksame Menge einer Verbindung nach Anspruch 1.

9. Mittel nach Anspruch 8 in einer für orale, parenterale, topische oder durch Inhalierung geeigneten Form, in dem der Wirkstoff

2-Hydroxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure oder

2-Hydroxy-3-(2-fluor-4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäure ist.

25 10. Arzneimittel zur Hemmung von antigen-induzierter Atmungs-Anaphylaxe, umfassend einen pharmazeutischen Träger oder ein Verdünnungsmittel und nicht-toxische Mengen einer Verbindung nach Anspruch 1, die zur Erzeugung der Hemmung ausreichen, und einen Histamin H₁-Rezeptor-Antagonisten.

11. Verbindung nach einem der Ansprüche 1 bis 7 zur Verwendung in der Therapie.

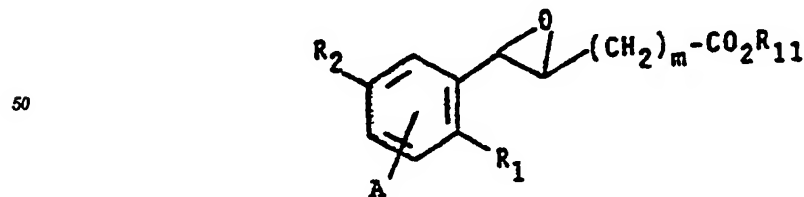
30 12. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, Formel (I), welches umfaßt die Umsetzung eines entsprechend geschützten substituierten Thiois, RSH, in dem R wie in Anspruch 1 definiert ist, mit:

(a) einer Verbindung der Formel



40 in der R₁ und R₂ wie in Anspruch 1 definiert sind, L eine austretende Gruppe, ausgewählt aus Chlor, Brom oder Hydroxy, bedeutet, Y CO₂R₁₀ oder CH(R₁₂)CO₂R₁₀ bedeutet, wobei R₁₀ eine Esterschutzgruppe bedeutet und R₁₂ Wasserstoff, Methyl, Methoxy oder Fluor darstellt, wobei Verbindungen gebildet werden, in denen Y CO₂H oder CH(R₁₂)CO₂H darstellt;

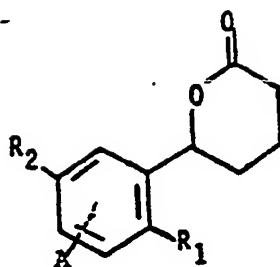
45 (b) einer Verbindung der Formel



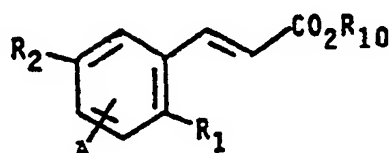
55

in der R₁, R₂ und m wie in Anspruch 1 definiert sind, und R₁₁ Niederalkyl bedeutet, wobei Verbindungen erhalten werden, in denen Y CH(OH)(CH₂)_mCO₂H bedeutet;

(c) einer Verbindung der Formel

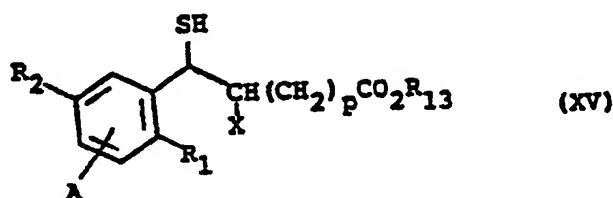


in der R_1 und R_2 wie in Anspruch 1 definiert sind, wobei Verbindungen erhalten werden, in denen Y $(CH_2)_3CO_2H$ bedeutet; und
(d) einer Verbindung der Formel



in der R_1 und R_2 wie in Anspruch 1 definiert sind und R_{10} eine Esterschutzgruppe bedeutet, wobei Verbindungen erhalten werden, in denen Y CH_2CO_2H bedeutet;
gefolgt von der Entfernung irgendwelcher Schutzgruppen, gegebenenfalls Auflösung irgendwelcher diastereomerer Verbindungsgemische und gegebenenfalls Herstellung eines pharmazeutisch verträglichen Salzes.

13. Verbindung der folgenden Strukturformel (XV)



in der

$R_1 (L)_a-(CH_2)_b-(T)_c-M$ bedeutet,

a 0 oder 1 ist;

b 3 bis 14 ist;

c 0 oder 1 ist;

L und T unabhängig Schwefel, Sauerstoff oder CH_2 bedeuten; und

M C_{1-6} -Alkyl, Ethinyl, Trifluormethyl, Isopropenyl, Furanyl, Thienyl, Cyclohexyl oder Phenyl, gegebenenfalls monosubstituiert mit Br, Cl, CF_3 , C_{1-4} -Alkoxy, C_{1-4} -Alkyl, Methylthio oder Trifluormethylthio, bedeutet;

R_2 und A unabhängig ausgewählt sind aus H, CF_3 , C_{1-4} -Alkyl, C_{1-4} -Alkoxy, F, Cl, Br, I, OH, NO_2 oder NH_2 ;

oder

R_1 und A H sind und

$R_2 (L)_a-(CH_2)_b-(T)_c-M$ bedeutet, wobei a, b, c, L, T und

M wie vorstehend definiert sind;

R_{13} C_{1-6} -Alkyl bedeutet;

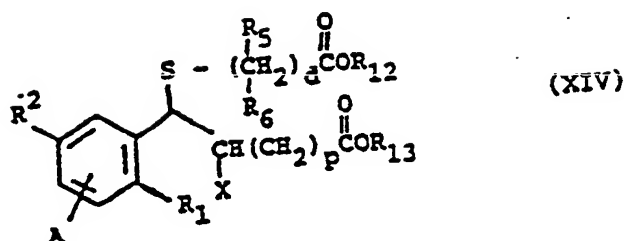
p 0, 1 oder 2 ist; und

X OH bedeutet.

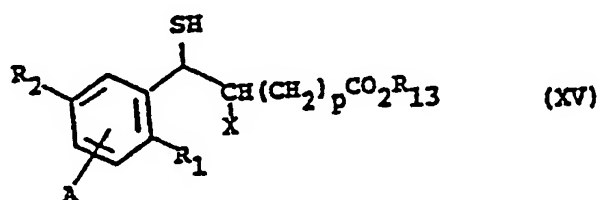
14. Verbindung nach Anspruch 13, nämlich 2-Hydroxy-3-mercapto-3-[2-(8-phenyloctyl)-phenyl]-propion-säuremethylester.

15. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, umfassend

(a) Umsetzung einer starken Base mit einer Verbindung der folgenden Strukturformel (XIV)



in der d 2 ist ; X OH ist, einer der Reste R₅ und R₆ benachbart zum Esterrest H ist und der andere H oder C₁₋₄-Alkyl bedeutet ; R₁, R₂, A und p wie in Anspruch 1 definiert sind und R₁₂ und R₁₃ unabhängig ausgewählt sind aus C₁₋₄-Alkyl, wobei ein Thiol der folgenden Strukturformel (XV) erhalten wird



in der R₁, R₂, R₁₃, A, X und p wie vorstehend für Formel (XIV) definiert sind ;

(b) Umsetzung des Thiols der Formel (XV) mit einem Alkylierungsmittel oder einem Michael-Akzeptor, wobei eine Verbindung der Formel (I) entsteht.

16. Verfahren nach Anspruch 15, wobei das Alkylierungsmittel ein Alkylhalogenid ist und die starke Base Natriumhydrid ist.

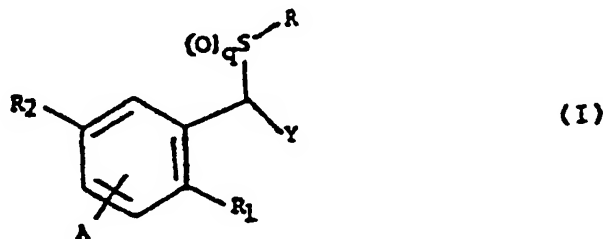
17. Verfahren nach Anspruch 15, wobei der Michael-Akzeptor eine α , β -ungesättigte Carbonylverbindung oder ein Alkin mit einer konjugierten Carbonylgruppe ist.

18. Verbindung nach Anspruch 2, nämlich 2-Hydroxy-3-(4-carbomethoxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäuremethylester ; 2-Hydroxy-3-(2-fluor-4-carbomethoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäuremethylester ; oder 2-Methoxy-3-(4-carbomethoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäuremethylester.

19. Verbindung nach einem der Ansprüche 1 bis 7 zur Verwendung bei der Behandlung von Erkrankungen, bei denen Leukotriene ein Faktor sind.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung von Verbindungen der folgenden Strukturformel (I)



in der

q 0, 1 oder 2 ist ;

R₁ (L)_a-(CH₂)_b-(T)_c-M bedeutet,

a 0 oder 1 ist ;

b 3 bis 14 ist ;

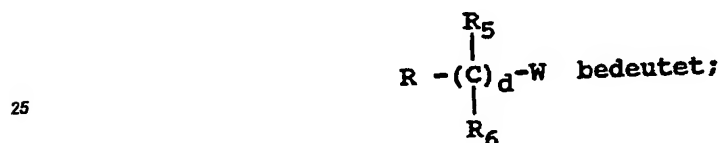
c 0 oder 1 ist ;

L und T unabhängig Schwefel, Sauerstoff oder CH₂ bedeuten, mit der Maßgabe, daß L und T nicht Schwefel

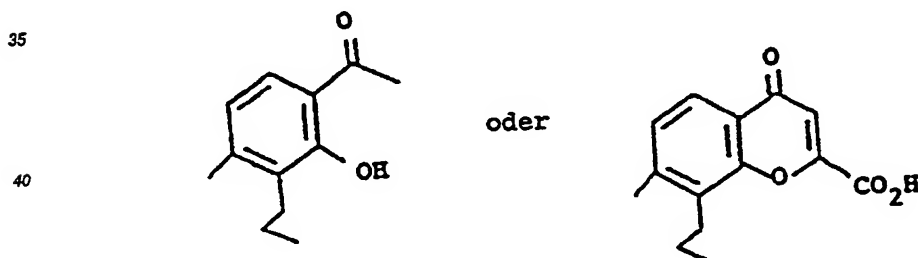
sind, wenn q 1 oder 2 ist; und
 M C₁₋₄-Alkyl, Ethinyl, Trifluormethyl, Isopropenyl, Furanyl, Thienyl, Cyclohexyl oder Phenyl, gegebenen-
 falls monosubstituiert mit Br, Cl, CF₃, C₁₋₄-Alkoxy, C₁₋₄-Alkyl, Methylthio oder Trifluomethylthio, bedeutet;
 R₂ und A unabhängig ausgewählt sind aus H, CF₃, C₁₋₄-Alkyl, C₁₋₄-Alkoxy, F, Cl, Br, I, OH, NO₂ oder NH₂;
 oder
 R₁ und A H sind und
 R₂ (L)_a-(CH₂)_b-(T)_c-M bedeutet, wobei a, b, c, L, T und M wie vorstehend definiert sind;
 Y COR₃ oder



bedeutet, wobei
 R₃ OH, NH₂, Aryloxy oder C₁₋₆-Alkoxy darstellt;
 n 0 oder 1 ist;
 p 0, 1 oder 2 ist;
 X H, OH, C₁₋₄-Alkyl, C₁₋₄-Alkoxy oder F bedeutet; und
 Z COR₃ oder Tetrazolyl bedeutet;



R₅ und R₆ unabhängig Wasserstoff oder C₁₋₄-Alkyl in jedem Fall bedeuten, wenn d nicht 0 ist;
 d 0 bis 6 ist;
 W einen sechsgliedrigen Aryl- oder Heteroarylring, ausgewählt aus Phenyl, Pyridyl oder Pyrimidyl, unsub-
 stituiert oder substituiert mit B, C oder D bedeutet; oder W eine der Formeln

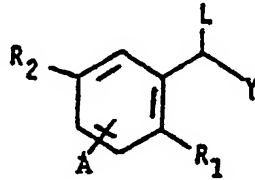


darstellt,

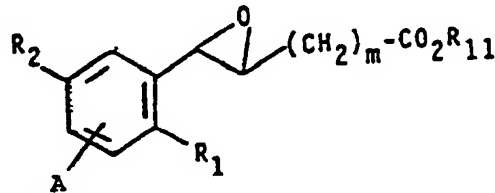


bedeutet, wobei
 R₅ und R₆ unabhängig Wasserstoff oder C₁₋₄-Alkyl darstellen, p 0 bis 6 ist; V H, C₁₋₄-Alkyl, COR₃, SO₃H,
 SO₂H, SO₂NH₂, COCH₂OH, CHOHCH₂OH oder Tetrazolyl bedeutet, wobei R₃ wie vorstehend definiert ist;
 C und D unabhängig ausgewählt sind aus H, OH, F, Cl, Br, CF₃, C₁₋₄-Alkyl, C₁₋₄-Alkoxy, Methylthio, Tri-

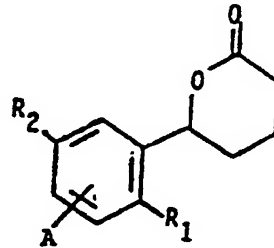
fluormethylthio, NO_2 , NH_2 , $\text{NHC}_{1-4}\text{-Alkyl}$ oder $\text{C}_{1-4}\text{-AlkylCO-}$;
 oder eines pharmazeutisch verträglichen Salzes davon, welches umfaßt die Umsetzung eines entsprechen-
 d geschützten substituierten Thiois, RSH , in dem R wie vorstehend definiert ist, mit :
 (a) einer Verbindung der Formel



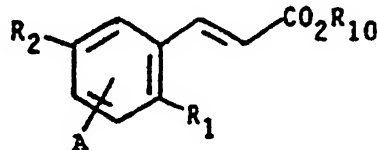
in der R_1 und R_2 wie vorstehend definiert sind, L eine austretende Gruppe, ausgewählt aus Chlor, Brom
 oder Hydroxy, bedeutet, Y CO_2R_{10} oder $\text{CH}(\text{R}_{12})\text{CO}_2\text{R}_{10}$ bedeutet, wobei R_{10} eine Esterschutzgruppe
 bedeutet und R_{12} Wasserstoff, Methyl oder Fluor darstellt, wobei Verbindungen gebildet werden, in denen
 Y CO_2H oder $\text{CH}(\text{R}_{12})\text{CO}_2\text{H}$ darstellt ;
 (b) einer Verbindung der Formel



in der R_1 , R_2 und m wie vorstehend definiert sind, und R_{11} Niederalkyl bedeutet, wobei Verbindungen erhal-
 ten werden, in denen Y $\text{CH}(\text{OH})(\text{CH}_2)_m\text{CO}_2\text{H}$ bedeutet ;
 (c) einer Verbindung der Formel



in der R_1 und R_2 wie vorstehend definiert sind, wobei Verbindungen erhalten werden, in denen Y
 $(\text{CH}_2)_3\text{CO}_2\text{H}$ bedeutet ; und
 (d) einer Verbindung der Formel



in der R_1 und R_2 wie vorstehend definiert sind und R_{10} eine Esterschutzgruppe bedeutet, wobei Verbin-
 dungen erhalten werden, in denen Y $\text{CH}_2\text{CO}_2\text{H}$ bedeutet ;
 gefolgt von der Entfernung irgendwelcher Schutzgruppen, gegebenenfalls Auflösung irgendwelcher dia-
 stereomerer Verbindungsgemische und gegebenenfalls Herstellung eines pharmazeutisch verträglichen

Salzes.

2. Verfahren nach Anspruch 1(b), bei dem trans-3-[2-(8-Phenylloctyl)-phenyl]-2,3-epoxypropionsäuremethylester und 4-Mercaptomethyl-3-methoxybenzoesäuremethylester zu 2-Hydroxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenylloctyl)-phenyl]-propionsäure umgesetzt werden.

3. Verfahren nach Anspruch 1(b), bei dem trans-3-[2-(8-Phenylloctyl)-phenyl]-2,3-epoxypropionsäuremethylester und p-Mercaptobenzoessäure zu 2-Hydroxy-3-(4-carbomethoxyphenylthio)-3-[2-(8-phenylloctyl)-phenyl]-propionsäuremethylester umgesetzt werden, welcher dann mit Natriumhydrid und Jodmethan zu 2-Methoxy-3-(4-carboxyphenylthio)-3-[2-(8-phenylloctyl)-phenyl]-propionsäure umgesetzt wird.

4. Verfahren nach Anspruch 1(b), bei dem trans-3-[2-(8-Phenylloctyl)-phenyl]-2,3-epoxypropionsäuremethylester und 2-Fluor-4-mercaptomethylbenzoesäuremethylester zu 2-Hydroxy-3-(2-fluor-4-carboxyphenylmethylthio)-3-[2-(8-phenylloctyl)-phenyl]-propionsäure umgesetzt werden.

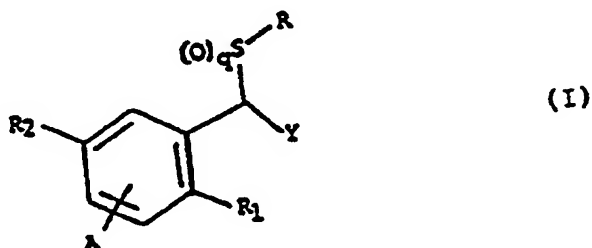
5. Verfahren nach Anspruch 3, bei dem das Erythro-Dia-stereomerengemisch aufgelöst wird, wobei 2(S)-Methoxy-3(R)-(4-carboxyphenylthio)-3-[2-(8-phenylloctyl)-phenyl]-propionsäure erhalten wird.

6. Verfahren nach den Ansprüchen 2, 3 oder 4, wobei das Produkt in sein Dinatriumsalz umgewandelt wird.

7. Verfahren zur Herstellung eines Arzneimittels, umfassend das Vermischen eines pharmazeutischen Trägers oder eines Verdünnungsmittels und einer Verbindung nach Anspruch 1, Formel (I).

8. Verfahren zur Herstellung eines Arzneimittels, umfassend das Vermischen eines pharmazeutischen Trägers oder eines Verdünnungsmittels, einer Verbindung nach Anspruch 1, Formel (I), und eines Histamin H₁-Rezeptor-Antagonisten.

9. Verfahren zur Herstellung einer Verbindung der folgenden Strukturformel (I)



in der

q 0, 1 oder 2 ist ;

R₁ (L)_a-(CH₂)_b-(T)_c-M bedeutet,

a 0 oder 1 ist ;

b 3 bis 14 ist ;

c 0 oder 1 ist ;

L und T unabhängig Schwefel, Sauerstoff oder CH₂ bedeuten, mit der Maßgabe, daß L und T nicht Schwefel sind, wenn q 1 oder 2 ist ; und

M C₁₋₄-Alkyl, Ethinyl, Trifluormethyl, Isopropenyl, Furanyl, Thienyl, Cyclohexyl oder Phenyl, gegebenenfalls monosubstituiert mit Br, Cl, CF₃, C₁₋₄-Alkoxy, C₁₋₄-Alkyl, Methylthio oder Trifluormethylthio, bedeutet;

R₂ und A unabhängig ausgewählt sind aus H, CF₃, C₁₋₄-Alkyl, C₁₋₄-Alkoxy, F, Cl, Br, I, OH, NO₂ oder NH₂;

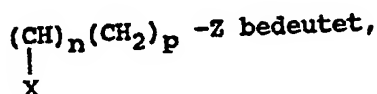
oder

R₁ und A H sind und

R₂ (L)_a-(CH₂)_b-(T)_c-M bedeutet, wobei a, b, c, L, T und

M wie vorstehend definiert sind ;

Y COR₃ oder



wobei

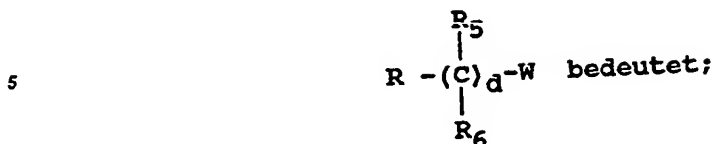
R₃ OH, NH₂, Aryloxy oder C₁₋₆-Alkoxy darstellt ;

n 0 oder 1 ist ;

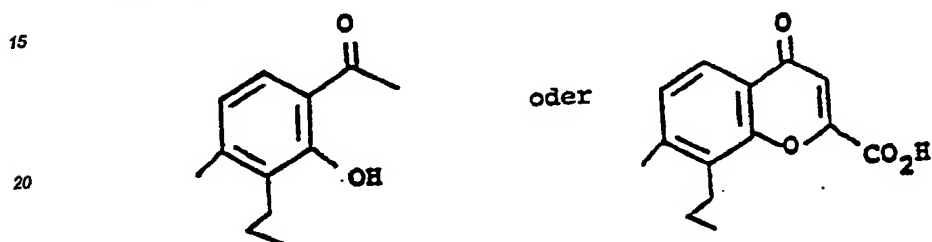
p 0, 1 oder 2 ist ;

X H, OH, C₁₋₄-Alkyl, C₁₋₄-Alkoxy oder F bedeutet ; und

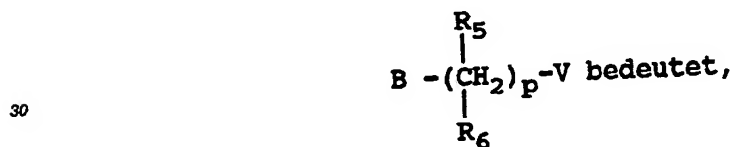
Z COR₃ oder Tetrazolyl bedeutet ;



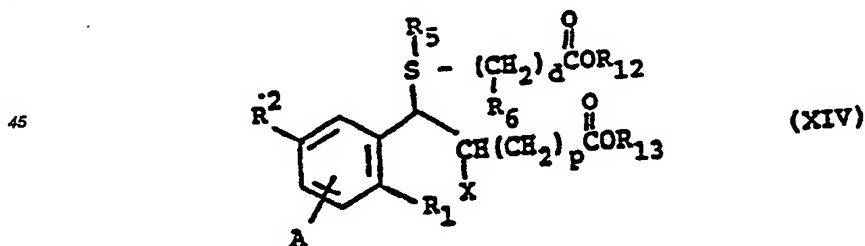
10 R₅ und R₆ unabhängig Wasserstoff oder C₁₋₄-Alkyl in jedem Fall bedeuten, wenn d nicht 0 ist ;
d 0 bis 6 ist ;
W einen sechsgliedrigen Aryl- oder Heteroaryling, ausgewählt aus Phenyl, Pyridyl oder Pyrimidyl, unsubstituiert oder substituiert mit B, C oder D bedeutet ; oder W eine der Formeln



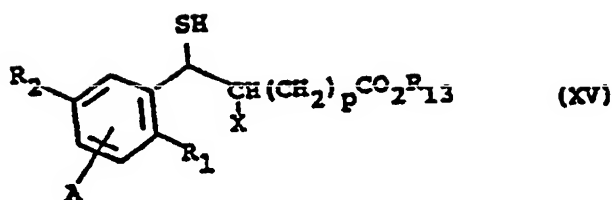
25 darstellt,



35 wobei
R₅ und R₆ unabhängig Wasserstoff oder C₁₋₄-Alkyl darstellen, p 0 bis 6 ist ; V H, C₁₋₄-Alkyl, COR₃, SO₃H, SO₂H, SO₂NH₂, COCH₂OH, CHOCH₂OH oder Tetrazolyl bedeutet, wobei R₃ wie vorstehend definiert ist ;
C und D unabhängig ausgewählt sind aus H, OH, F, Cl, Br, CF₃, C₁₋₄-Alkyl, C₁₋₄-Alkoxy, Methylthio, Tri-
fluormethylthio, NO₂, NH₂, NHC₁₋₄-Alkyl oder C₁₋₄-AlkylCO— ;
40 oder eines pharmazeutisch verträglichen Salzes davon, umfassend
(a) Umsetzung einer starken Base mit einer Verbindung der folgenden Strukturformel (XIV)



55 in der d 2 ist ; X OH ist, einer der Reste R₅ und R₆ benachbart zum Esterrest H ist und der andere H oder C₁₋₄-Alkyl bedeutet ; R₁, R₂, A und p wie vorstehend definiert sind und R₁₂ und R₁₃ unabhängig ausgewählt sind aus C₁₋₄-Alkyl, wobei ein Thiol der folgenden Strukturformel (XV) erhalten wird



in der R_1 , R_2 , R_{13} , A, X und p wie vorstehend für Formel (XIV) definiert sind ;

(b) Umsetzung des Thioms der Formel (XV) mit einem Alkylierungsmittel oder einem Michael-Akzeptor, wobei eine Verbindung der Formel (I) entsteht.

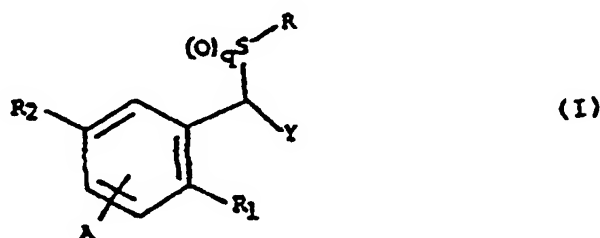
10. Verfahren nach Anspruch 9, wobei das Alkylierungsmittel ein Alkylhalogenid ist.

11. Verfahren nach Anspruch 9, wobei die starke Base Natriumhydrid ist.

12. Verfahren nach Anspruch 9, wobei der Michael-Akzeptor eine α , β -ungesättigte Carbonylverbindung oder ein Alkin mit einer konjugierten Carbonylgruppe ist.

Patentansprüche für folgenden Vertragsstaat : GR

1. Verfahren zur Herstellung von Verbindungen der folgenden Strukturformel (I)



in der

q 0, 1 oder 2 ist ;

$R_1 (L)_a (CH_2)_b (T)_c - M$ bedeutet,

a 0 oder 1 ist ;

b 3 bis 14 ist ;

c 0 oder 1 ist ;

L und T unabhängig Schwefel, Sauerstoff oder CH_2 bedeuten, mit der Maßgabe, daß L und T nicht Schwefel sind, wenn q 1 oder 2 ist ; und

M C_{1-4} -Alkyl, Ethinyl, Trifluormethyl, Isopropenyl, Furanyl, Thienyl, Cyclohexyl oder Phenyl, gegebenenfalls monosubstituiert mit Br, Cl, CF_3 , C_{1-4} -Alkoxy, C_{1-4} -Alkyl, Methylthio oder Trifluormethylthio, bedeutet ;

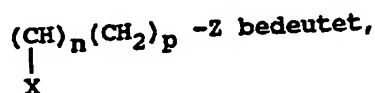
R_2 und A unabhängig ausgewählt sind aus H, CF_3 , C_{1-4} -Alkyl, C_{1-4} -Alkoxy, F, Cl, Br, I, OH, NO_2 oder NH_2 ;

oder

R_1 und A H sind und

$R_2 (L)_a (CH_2)_b (T)_c - M$ bedeutet, wobei a, b, c, L, T und M wie vorstehend definiert sind ;

Y COR_3 oder



wobei

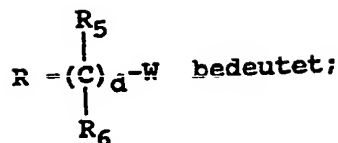
R_3 OH, NH_2 , Aryloxy oder C_{1-6} -Alkoxy darstellt ;

n 0 oder 1 ist ;

p 0, 1 oder 2 ist ;

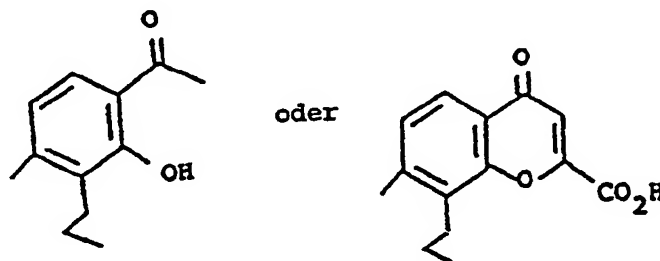
X H, OH, C_{1-4} -Alkyl, C_{1-4} -Alkoxy oder F bedeutet ; und

Z COR_3 oder Tetrazolyl bedeutet ;

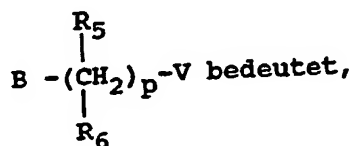


R_5 und R_6 unabhängig Wasserstoff oder C_{1-4} -Alkyl in jedem Fall bedeuten, wenn d nicht 0 ist ;
 d 0 bis 6 ist ;

W einen sechsgliedrigen Aryl- oder Heteroarylring, ausgewählt aus Phenyl, Pyridyl oder Pyrimidyl, unsubstituiert oder substituiert mit B, C oder D bedeutet ; oder W eine der Formeln



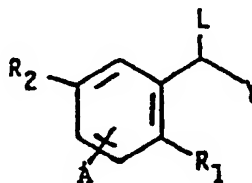
darstellt,



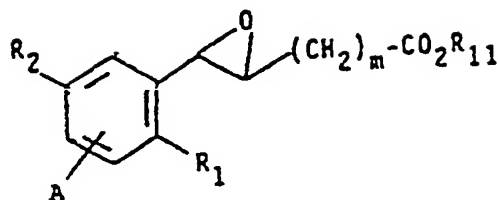
wobei

R_5 und R_6 unabhängig Wasserstoff oder C_{1-4} -Alkyl darstellen, p 0 bis 6 ist ; V H, C_{1-4} -Alkyl, COR_3 , SO_3H , SO_2H , SO_2NH_2 , $COCH_2OH$, $CHOHCH_2OH$ oder Tetrazolyl bedeutet, wobei R_3 wie vorstehend definiert ist ;
 C und D unabhängig ausgewählt sind aus H, OH, F, Cl, Br, CF_3 , C_{1-4} -Alkyl, C_{1-4} -Alkoxy, Methylthio, Trifluormethylthio, NO_2 , NH_2 , NHC_{1-4} -Alkyl oder C_{1-4} -AlkylCO— ;
 oder eines pharmazeutisch verträglichen Salzes davon, welches umfaßt die Umsetzung eines entsprechend geschützten substituierten Thiols, RSH , in dem R wie vorstehend definiert ist, mit :

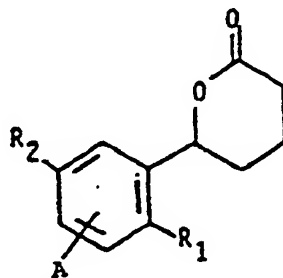
(a) einer Verbindung der Formel



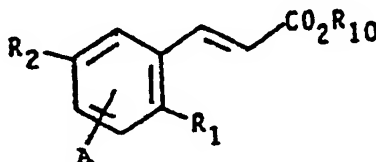
In der R_1 und R_2 wie vorstehend definiert sind, L eine austretende Gruppe, ausgewählt aus Chlor, Brom oder Hydroxy, bedeutet, Y CO_2R_{10} oder $CH(R_{12})CO_2R_{10}$ bedeutet, wobei R_{10} eine Esterschutzgruppe bedeutet und R_{12} Wasserstoff, Methyl oder Fluor darstellt, wobei Verbindungen gebildet werden, in denen
 (b) einer Verbindung der Formel



in der R_1 , R_2 und m wie vorstehend definiert sind, und R_{11} Niederalkyl bedeutet, wobei Verbindungen erhalten werden, in denen Y $CH(OH)(CH_2)_mCO_2H$ bedeutet ;
(c) einer Verbindung der Formel



in der R_1 und R_2 wie vorstehend definiert sind, wobei Verbindungen erhalten werden, in denen Y $(CH_2)_3CO_2H$ bedeutet ; und
(d) einer Verbindung der Formel



in der R_1 und R_2 wie vorstehend definiert sind und R_{10} eine Esterschutzgruppe bedeutet, wobei Verbindungen erhalten werden, in denen Y CH_2CO_2H bedeutet ;
gefolgt von der Entfernung irgendwelcher Schutzgruppen, gegebenenfalls Auflösung irgendwelcher diastereomerer Verbindungsgemische und gegebenenfalls Herstellung eines pharmazeutisch verträglichen Salzes.

2. Verfahren nach Anspruch 1(b), bei dem trans-3-[2-(8-Phenyloctyl)-phenyl]-2,3-epoxypropionsäuremethylester und 4-Mercaptomethyl-3-methoxybenzoesäuremethylester zu 2-Hydroxy-3-(4-carboxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)-phenyl]-propionsäure umgesetzt werden.

3. Verfahren nach Anspruch 1(b), bei dem trans-3-[2-(8-Phenyloctyl)-phenyl]-2,3-epoxypropionsäuremethylester und p-Mercaptobenzoesäure zu 2-Hydroxy-3-(4-carbomethoxyphenylthio)-3-[2-(8-phenyloctyl)-phenyl]-propionsäuremethylester umgesetzt werden, welcher dann mit Natrium-hydrid und Jodmethan zu 2-Methoxy-3-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)-phenyl]-propionsäure umgesetzt wird.

4. Verfahren nach Anspruch 1(b), bei dem trans-3-[2-(8-Phenyloctyl)-phenyl]-2,3-epoxypropionsäuremethylester und 2-Fluor-4-mercaptomethylbenzoesäuremethylester zu 2-Hydroxy-3-(2-fluor-4-carboxyphenylmethylthio)-3-[2-(8-phenyloctyl)-phenyl]-propionsäure umgesetzt werden.

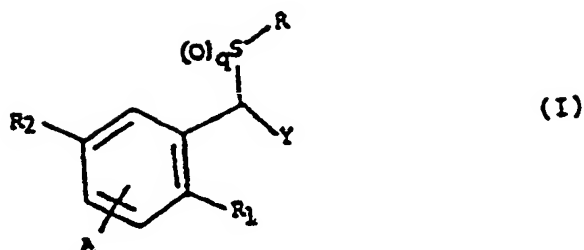
5. Verfahren nach Anspruch 3, bei dem das Erythro-Dia-stereomerengemisch aufgelöst wird, wobei 2(S)-Methoxy-3-(R)-(4-carboxyphenylthio)-3-[2-(8-phenyloctyl)-phenyl]-propionsäure erhalten wird.

6. Verfahren nach den Ansprüchen 2, 3 oder 4, wobei das Produkt in sein Dinatriumsalz umgewandelt wird.

7. Verfahren zur Herstellung eines Arzneimittels, umfassend das Vermischen eines pharmazeutischen Trägers oder eines Verdünnungsmittels und einer Verbindung nach Anspruch 1, Formel (I).

8. Verfahren zur Herstellung eines Arzneimittels, umfassend das Vermischen eines pharmazeutischen Trägers oder eines Verdünnungsmittels, einer Verbindung nach Anspruch 1, Formel (I), und eines Histamin H_1 -Rezeptor-Antagonisten.

9. Verfahren zur Herstellung einer Verbindung der folgenden Strukturformel (I)



in der

q 0, 1 oder 2 ist ;

R₁ (L)_a-(CH₂)_b-(T)_c-M bedeutet,

a 0 oder 1 ist ;

b 3 bis 14 ist ;

c 0 oder 1 ist ;

L und T unabhängig Schwefel, Sauerstoff oder CH₂ bedeuten, mit der Maßgabe, daß L und T nicht Schwefel sind, wenn q 1 oder 2 ist ; und

M C₁₋₄-Alkyl, Ethinyl, Trifluormethyl, Isopropenyl, Furanyl, Thienyl, Cyclohexyl oder Phenyl, gegebenenfalls monosubstituiert mit Br, Cl, CF₃, C₁₋₄-Alkoxy, C₁₋₄-Alkyl, Methylthio oder Trifluormethylthio, bedeutet ;

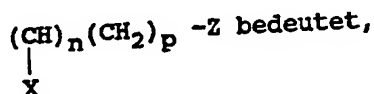
R₂ und A unabhängig ausgewählt sind aus H, CF₃, C₁₋₄-Alkyl, C₁₋₄-Alkoxy, F, Cl, Br, I, OH, NO₂ oder NH₂ ;

oder R₁ und A H sind und

R₂ (L)_a-(CH₂)_b-(T)_c-M bedeutet, wobei a, b, c, L, T und

M wie vorstehend definiert sind ;

Y COR₃ oder



wobei

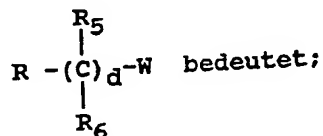
R₃ OH, NH₂, Aryloxy oder C₁₋₆-Alkoxy darstellt ;

n 0 oder 1 ist ;

p 0, 1 oder 2 ist ;

X H, OH, C₁₋₄-Alkyl, C₁₋₄-Alkoxy oder F bedeutet ; und

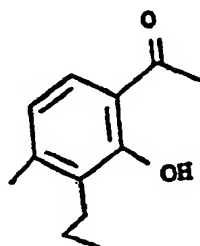
Z COR₃ oder Tetrazolyl bedeutet ;



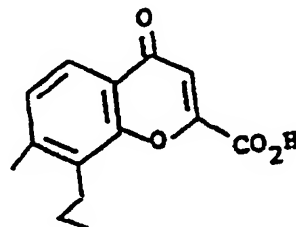
R₅ und R₆ unabhängig Wasserstoff oder C₁₋₄-Alkyl in jedem Fall bedeuten, wenn d nicht 0 ist ;

d 0 bis 6 ist ;

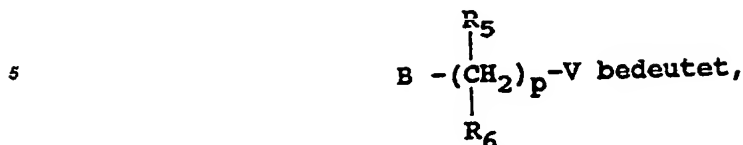
W einen sechsgliedrigen Aryl- oder Heteroarylring, ausgewählt aus Phenyl, Pyridyl oder Pyrimidyl, unsubstituiert oder substituiert mit B, C oder D bedeutet ; oder W eine der Formeln



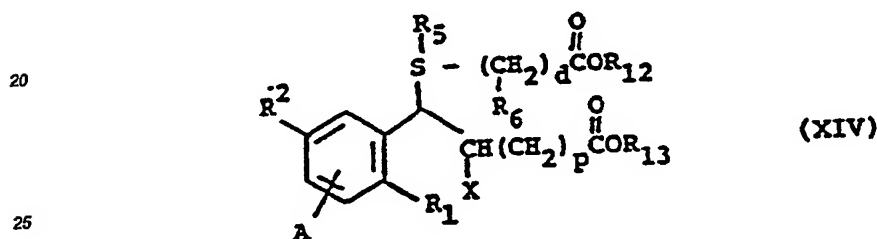
oder



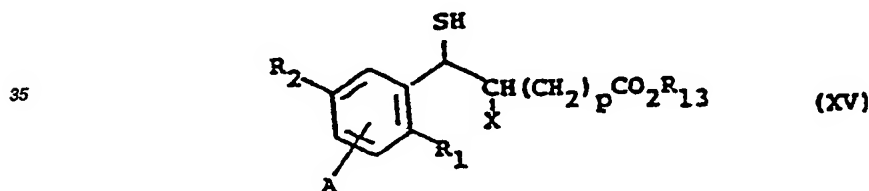
darstellt,



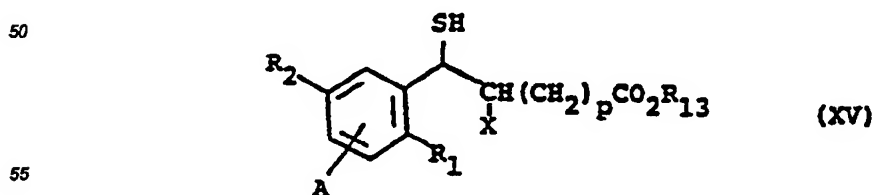
10 wobei
 R_5 und R_6 unabhängig Wasserstoff oder C_{1-4} -Alkyl darstellen, p 0 bis 6 ist; V H, C_{1-4} -Alkyl, COR_3 , SO_3H ,
 SO_2H , SO_2NH_2 , $COCH_2OH$, $CHOHCH_2OH$ oder Tetrazolyl bedeutet, wobei R_3 wie vorstehend definiert ist;
 C und D unabhängig ausgewählt sind aus H, OH, F, Cl, Br, CF_3 , C_{1-4} -Alkyl, C_{1-4} -Alkoxy, Methylthio, Tri-
15 fluormethylthio, NO_2 , NH_2 , NHC_{1-4} -Alkyl oder C_{1-4} -AlkylCO—;
oder eines pharmazeutisch verträglichen Salzes davon, umfassend
(a) Umsetzung einer starken Base mit einer Verbindung der folgenden Strukturformel (XIV)



30 in der d 2 ist; X OH ist, einer der Reste R_5 und R_6 benachbart zum Esterrest H ist und der andere H oder
 C_{1-4} -Alkyl bedeutet; R_1 , R_2 , A und p wie vorstehend definiert sind und R_{12} und R_{13} unabhängig ausgewählt
sind aus C_{1-4} -Alkyl, wobei ein Thiol der folgenden Strukturformel (XV) erhalten wird



45 in der R_1 , R_2 , R_{13} , A, X und p wie vorstehend für Formel (XIV) definiert sind;
(b) Umsetzung des Thiols der Formel (XV) mit einem Alkylierungsmittel oder einem Michael-Akzeptor,
wobei eine Verbindung der Formel (I) entsteht.
10. Verfahren nach Anspruch 9, wobei das Alkylierungsmittel ein Alkylhalogenid ist.
11. Verfahren nach Anspruch 9, wobei die starke Base Natriumhydrid ist.
12. Verfahren nach Anspruch 9, wobei der Michael-Akzeptor eine α , β -ungesättigte Carbonylverbindung
oder ein Alkin mit einer konjugierten Carbonylgruppe ist.
13. Verbindung der folgenden Strukturformel (XV)



in der

$R_1 (L)_a (CH_2)_b (T)_c - M$ bedeutet,

a 0 oder 1 ist ;

b 3 bis 14 ist ;

c 0 oder 1 ist ;

5 L und T unabhängig Schwefel, Sauerstoff oder CH_2 bedeuten ; und
 M C_{1-4} -Alkyl, Ethinyl, Trifluormethyl, Isopropenyl, Furanyl, Thienyl, Cyclohexyl oder Phenyl, gegebenenfalls monosubstituiert mit Br, Cl, CF_3 , C_{1-4} -Alkoxy, C_{1-4} -Alkyl, Methylthio oder Trifluormethylthio, bedeutet;
 R_2 und A unabhängig ausgewählt sind aus H, CF_3 , C_{1-4} -Alkyl, C_{1-4} -Alkoxy, F, Cl, Br, I, OH, NO_2 oder NH_2 ;
 oder

10 R_1 und A H sind und
 $R_2 (L)_a (CH_2)_b (T)_c - M$ bedeutet, wobei a, b, c, L, T und
 M wie vorstehend definiert sind ;

R_{13} C_{1-8} -Alkyl bedeutet ;

p 0, 1 oder 2 ist ; und

15 X OH bedeutet

14. Verbindung nach Anspruch 13, nämlich 2-Hydroxy-3-mercapto-3-[2-(8-phenyloctyl)-phenyl]-propionsäuremethylester.

15. Verbindung nämlich

2-Hydroxy-3-(4-carbomethoxy-2-methoxyphenylmethylthio)-3-[2-(8-phenyloctyl)phenyl]propionsäuremethylester ;
 20 2-Hydroxy-3-(2-fluor-4-carbomethoxyphenylmethylthio)-3-[2-(8-phenyloctyl) phenyl]-propionsäuremethylester ; oder
 2-Methoxy-3-(4-carbomethoxyphenylthio)-3-[2-(8-phenyloctyl)-phenyl]-propionsäuremethylester.

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